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(54) Title: MODIFIED SEED STORAGE PROTEINS

(57) Abstract

The invention provides modified plant storage proteins, in which the modification is effected in the primary structure of the protein, and the tertiary and quaternary structure of the protein is retained. The site for modification is selected by reference to the three-dimensional structure of the protein, which has been newly established by the inventors. Modified DNA molecules, vectors, transgenic plants, and parts and products thereof are also claimed.

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MODIFIED SEED STORAGE PROTEINS

This invention relates to plant seed storage proteins, and in particular to methods of modifying said proteins at specific sites.

Background of the Invention

Over the last few years there has been dramatic

10 progress in the development of gene transfer systems for higher plants, and systems are now available for monocotyledonous plants, as well as for a variety of dicotyledonous plants. It is now possible not only to introduce foreign genes (including non-plant genes) into plant cells and tissues, and to regenerate whole plants, but also to

control the site in the plant where such genes will be expressed. Methods for introducing genes into plants, and the prospects which these methods offer for applying genetic engineering methods to improvement of crops, have recently been reviewed (C.S. Gasser and R.T. Fraley (1989) Science 244 1293-1299); this review reflects the state of the art. International Patent Application No. WO/8903887 discloses a process for production of a mammalian peptide via expression of a modified seed storage protein gene in a transgenic plant.

10 The most commonly used vector is Agrobacterium tumefaciens Ti plasmid, which is successful in transferring genetic information into a variety of dicotyledonous plants, including peas and beans. More recently, the plant virus geminivirus

has been proposed as a general purpose vector for use with 15 plants (Australian Patent Application No. 599609 (64380/86) by Monsanto Company and David Bisaro)

Genetic engineering of improved grain crops has been hampered by the lack of detailed structural information about functional storage proteins, which form the major protein 20 component of plant seeds¹. After synthesis and processing, these proteins are transported to membranous organelles, known as protein bodies, where they accumulate in large amounts²⁻⁴. Upon germination, they are degraded by endogenous proteases to provide nutrition for the growing plant⁵. Because of the high 25 level of expression and subsequent accumulation of these proteins, they determine the nutritional value of the seed and dictate the requirement for supplements when the seed is used as foodstuff for man or domestic animals.

Most of the protein found in mature seeds belongs to 30 a class called the seed storage proteins. This term is used to describe those proteins whose function is to provide, upon germination, a source of fixed carbon and nitrogen to sustain the early heterotrophic growth of the seedling. However, it is because of the importance of seeds to human nourishment 35 that so much work has been directed at understanding seed proteins. Among the best characterised of the seed proteins

WO 91/04270 PCT/AU90/00430 - 3 -

are those from the agriculturally important legumes, soya bean (Glycine max), garden pea (Pisum sativum) and French bean (Phaseolus vulgaris), although increasing attention is being given to food crops of the Third World, including cow pea 5 (Vigna unguiculata), mung bean (V. radiata) and pigeon pea (Cajanus cajan).

As a whole, legume storage proteins, which are mostly of the salt-soluble globulin class, are a nutritionally-poor source of tryptophan and the sulphur-10 containing amino acids, methionine and cysteine, although some of the other protein fractions within the seed (for example the albumins) may have adequate levels of these essential amino acids. Much effort has been directed to improving the understanding of storage proteins so as to be able to 15 manipulate their genes using methods such as recombinant DNA techniques, tissue culture and plant breeding in such a way as to enhance the nutritional value of seed proteins for human and other monogastric animals.

There are two major types of storage proteins in 20 legume seeds, known respectively as vicilins and legumins, which are distinguishable by their sedimentation coefficients (75/11S), oligomeric organisation (trimeric/hexameric) and polypeptide chain structure (single chain/disulphide linked pair of chains) 6-12. Both types are found within an 25 individual storage body 13,14. Analysis of amino-acid sequence data from these two classes suggests that they may be evolutionarily and structurally related 15,16. Clear sequence relationships have been established within the classes 12. Furthermore, a sequence motif common to legumins and 30 vicilins 15 has been found to occur twice in vicilins 16, suggesting a repeated structural motif in vicilins. Genes encoding two vicilin-type proteins have been isolated from pea (Pisum sativum), and transgenically

expressed in tobacco, and their regulatory DNA sequence 35 elements have been identified; these sequences respectively govern the specificity of expression and level of transcription (Newbigin, E.J. and T.J.V. Higgins: Proc. 8th Australian Biotechnology Conference, Sydney 1989, 104-109)

Attempts have been made to improve the functional 5 properties and nutritional value of glycinin, one of the major storage proteins of soybean, by producing cDNAs encoding glycinins modified by deletion of subsequences and by addition of sequences encoding four continuous methionines. The authors have shown expression and accumulation of some of the 10 mutant proteins in <u>E. coli</u> cells (Kim et al., 1990).

However, their result is inconclusive, at best preliminary, as no attempt is made at expression in plant systems. Furthermore, these authors were limited in that they could only make changes to highly variable regions of the sequence, and then only in an ad hoc fashion. Their methods cannot be generally applied across a spectrum of legumins or vicilins. Indeed, the regions they have modified are regions of low homology to the vicilins, and therefore of no immediate application to vicilins. Nevertheless, their work does underscore that it is realistic to make modified seed storage

Another seed storage protein, arcelin, has been identified in certain wild forms of <u>Phaseolus vulgaris</u> (Romero 25 A. et al (1986) Theor. Appl. Genet <u>72</u> 123-128; Osborn et al. (1986) Theor. Appl. Genet. <u>71</u> 847-855); these proteins are toxic to bruchid pests of beans, and transfer of the cloned arcelin gene to other bean plant confers insect resistance (European Patent Application No. 337750: The Plant Cell 30 Research Institute Inc).

proteins with improved properties according to the present

invention.

In order to enable us to engineer novel properties into seeds without prejudicing their performance in vivo, we have for the first time determined the three-dimensional structure of phaseolin, the major 7S storage protein from the 35 French Bean Phaseolus vulgaris. With this structural information, we can select suitable sites for modification.

Specific protein engineering targets in this system include improved nutritional value, altered stability with respect to functionality in food systems, and general use as a high-level expression system.

Phaseolin, a vicilin-like molecule, is a trimer of three similar glycosylated polypeptides of molecular weights around 50 000¹⁷. Unlike other vicilins, the phaseolin trimer (M_r about 150 000) associates into a dodecamer 18 below pH 4.5.

Because of the sequence and structural relationships 10 between vicilins and legumins referred to above and further discussed hereinafter, we consider that phaseolin is a suitable model for legume 7S and 11S storage proteins in particular, and seed storage 7S and 11S proteins in general. Phaseolin has been expressed in transgenic plants 45.

- 15 Madison et al. have recently used the three-dimensional structure of the complex between trypsin and bovine pancreatic tissue inhibitor to predict the site of interaction between tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1). Although the
- 20 three-dimensional structures of tPA and PAI-1 are not known, tPA and trypsin have sequence similarities. Using these similarities, the authors identified a loop, and one particular residue within the loop, which forms part of the interactive surface between PAI-1 and tPA; by changing the
- 25 sequence of this loop by site-directed mutagenesis, they produced tPA which was less susceptible to inhibition (E.L. Madison, E.J. Goldsmith, R.D. Gerard, M-J.H. Gething, and J.F. Sambrook (1989) Nature 339 721-724).

This strongly suggests that the three-dimensional 30 structure of phaseolin can be used to predict the three-dimensional structures of other vicilins and of legumins.

We have found that the polypeptides of the trimeric seed storage protein phaseolin comprise two

35 structurally-similar units each made up of a β -barrel and an κ -helical domain. The β -barrel has the "jelly-roll" folding

WO 91/04270 PCT/AU90/00430

topology shown by viral coat proteins and the &-helical domain shows structural similarity to the helix-turn-helix motif found in certain DNA-binding proteins. The tetramer of trimers referred to above turns out to be the form of the 5 molecule in the crystals studied here.

Current experience suggests that protein structure is remarkably stable to manipulation by site-directed mutagenesis. Moreover, functional properties of α/β barrel proteins, 8-stranded β -barrel enzymes, and four-helix 10 frameworks are stable to insertions and other modifications (reviewed by D. Ringe (1989) Nature 339 658-9).

Summary of the Invention

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The major barrier to modifying plants to produce seed storage proteins with commercially desirable properties 15 is knowledge of the three-dimensional structure of the storage proteins.

We have now determined the three-dimensional structure of a representative seed storage protein, phaseolin. Current knowledge in the construction of transgenic plants, 20 and in protein structure and engineering, enables us to use this three-dimensional structure to select target sites in the structure for one or more of the following modifications:

- (a) introduction of point mutations;
- (b) deleting or inserting sequences;
- (c) adding glycosylation sites;
 - (d) introducing disulphide bonds.

Thus, based on the three-dimensional structure disclosed herein, and experimental protocols known to persons skilled in the art, the following modifications can be made:

- 30 (i) Introduction of new N-linked glycosylation sites for altering the stability and/or solubility of the protein;
 - (ii) Substitution of internal amino acids by methionine to raise the sulphur content of the seed;

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- (iii) Truncation of protease-susceptible loops on the structure to improve stability;
- (iv) Introduction of protease-labile loops to improve the digestive properties;
- (v) Introduction of disulphide bonds or other stabilising mutations to protect the storage protein structure on passage through the rumen to improve the nutritional value of the protein for ruminants;
- 10 (vi) Introduction of heterologous protein or peptide sequences into the structure to enable their production in crops; and
 - (vii) Modifications to the sequence to enhance resistance of the seeds or products thereof to pests such as insects.

Aspects of these properties that are relevant in food systems include:

- (a) stability and pH solubility for the large scale extraction of the proteins from seeds;
- 20 (b) acid solubility for protein enriched beverages;
 - (c) thermostability for heat-setting properties in snack foods; and
- (d) amino acid composition for nutritional balance.

In one aspect, the present invention provides a mutein which is a variant of a naturally-occurring legume seed storage protein, wherein said mutein has a modified primary structure relative to said legume storage protein, but retains 30 the tertiary and quaternary structure of said legume storage protein.

For the purposes of this specification, retention of the tertiary and quaternary structure is to be understood to mean that elements of that tertiary and quaternary structure 35 which are not the subject of primary structure modifications are substantially unaffected by said modifications.

Thus according to one preferred embodiment of the present invention there is provided a plant 7S or 1lS storage protein modified at a specific amino acid residue or a specific region of its amino acid sequence, wherein the tertiary and quarternary structure of the naturally occurring storage protein is retained.

Preferably the modification is selected from the group consisting of:

- (a) introduction of one or more point mutations;
- (b) deletion of one or more defined sequences of amino acids;
 - (c) insertion of one or more defined sequences of amino acids;
- (d) introduction of one or more glycosylation 15 sites; and
 - (e) introduction of one or more disulphide bonds. More preferably the modification is selected from the group consisting of:
 - (a) introduction of N-linked glycosylation sites;
- 20 (b) substitution of internal amino acids by methionine;
 - (c) truncation of protease-labile loops; and
 - (d) introduction of protease-labile loops.
- According to a second aspect of the invention, there
 25 is provided a DNA molecule whose sequence encodes a mutein, as
 defined above. Preferably this DNA encodes a protein having
 the properties of a plant 7S or 1lS storage protein, and also
 encodes one or more of the modifications set out above.
 Plasmids, expression vectors, and microorganisms comprising
 30 said DNA are also within the scope of the invention.

According to a third aspect of the invention there is provided a transgenic plant or part thereof having a DNA sequence as defined above.

Preferably the plant part is a seed.

It will be evident to the person skilled in the art that the changes to the seed storage proteins provided by the method according to the invention will have to be made in the first instance at the DNA level. The modified DNA thus represents the initial embodiment of the changes; such DNA will be converted, via the processes of transcription and translation in the cell, to yield the modified seed storage protein.

Brief Description of the Drawings

10 Figure 1 (25 sheets) represents the atomic co-ordinates of phaseolin in orthogonal A units. The three-fold symmetry axis of the phaseolin trimer is coincident with the Y axis of the co-ordinate frame. The coordinates of the C atoms have been deposited by the applicant in the 15 Brookhaven Protein Data Bank.

Figure 2 represents schematic diagrams showing the two observed patterns of interaction between the $\kappa + /5$ structural units. The absence of residues 213-219 in the electron density map leaves an ambiguity as to which is the 20 correct pairing of the $\kappa + /5$ units to form the polypeptide.

(a) represents the preferred polypeptide (see text). In both diagrams the view is down the molecular three-fold axis and from the centre of the tetramer outwards. The pseudo-diads relating the structural units lie in the plane of the paper, 25 intersecting the molecular three-fold.

Figure 3 represents a stereo pair showing a C α trace of the phaseolin trimer, viewed down the molecular three-fold towards the centre of the tetramer. The N- and C-termini of each subunit are labelled. The two possible ways 30 of linking the two $\alpha+\beta$ units to form the subunit are indicated: the shorter link of 17Å (solid line) is favoured above the longer 34Å link (dashed line). The figure was drawn using a computer program written by Lesk and Hardman 31 .

Figure 4 is a diagram showing the structure of native phaseolin (A) and the proposed high-methionine mutant phaseolin (B) in the neighbourhood of residues 84 to 88. The methionine sidechains of the mutant are seen to be accommodated in the structure without disruption to the tertiary or quaternary structure of the protein. For clarity, residues in the same \(\beta\)-sheet as residues 84 to 88 are not shown.

Figure 5 is a diagram showing the structure of

10 native phaseolin (A) and the proposed high-methionine mutant
phaseolin (B) in the neighbourhood of residues 261-265. The
methionine sidechains of the mutant are seen to be
accommodated in the structure without disruption to the
tertiary and quaternary structure of the protein. For

15 clarity, residues in the same /-sheet as residues 261-265 are
not shown.

Structure Description

x-ray diffraction data to 3Å resolution were collected from Type II crystals of phaseolin 19 and heavy atom 20 derivatives. The methods of analysis do not form part of this invention. However, various attempts to solve the structure by multiple isomorphous replacement and non-crystallographic symmetry averaging were unsuccessful over a period of 6 years, until a cautious approach using phase extension procedures was 25 adopted.

Structural heterogeneity

Three different genes encoding potential protein products have been identified by gene sequencing 11. These differ only in number of amino acids, and contain 397, 411 and 30 412 amino acids respectively, after allowing for cleavage of a 24 amino-acid signal sequence. The sequence and numbering used here is given in Table 1.

1	TSLREEEESQD	NPFYFNSDNS	A' WNTLFKNQY βββββ	<u>A</u> GHIRVLQRFDQQ ββββββ	SKRLQNLEDYI	B RLVEFRSK BBBBBBB.	60
61	C PETLLLPQQAD βββββββ.	<u>D</u> AELLLVVRSG ββββββββ.Ι	<u>E</u> SAILVLVKPI .ββββββ	<u>F</u> DDRREYFFLTSDI ββββββββ.	<u>G</u> NPIFSDHQKIF Vβββ	H PAGTIFYL \$\$\$\$\$	120
121	VNRDPKEDLRI ββββ	I IQLAMPVNNP βββββ	<u>J</u> QIHEFFLSS1 βΙββ	1 TEAQQSYLQEFSI	<u>2</u> CHILEASFNSK XaaaaaaaaI.a	3 FEEINRV aaaaaaa	180
181	LFEEEGQQEGV	IVNIDSEQIK	4 ELSKHAKSSS Qaaaaaaaaa	A' FRKSLSKQDNTIG Ca[V] ββββ	A GNEFGNLTERT DGβββββ		240
241	B ISSIEMEEGALE ββββββββΙββ	C TVPHYYSKAIV BBBBBBBB	 VILVVNEGEA Ββββββββ	<u>E</u> HVELVGPKGNKE ββββV.	F TLEYESYRAE βββββ	<u>G</u> LSKDDVF : βββ	300
301	<u>Η</u> VIPAAYPVAIKA ββββββ.	<u>I</u> TSNVNFTGFG ββGβββββ	J SINANNNRN 18888	<u>1</u> LLAGKTDNVISS ββ.Ιαααα	IGRALDGKDVI	GLTFSG 3	360
361	3 SGDEVMKLINKQ . aaaaaaaaaaa.		HQQEQQKGRI	KGAFVY]			

Table 1. Amino-acid sequence of the shorter (397 residue) β -type phaseolin polypeptide. The line underneath the sequence contains the following symbols. α : regions of α -helical secondary structure, β : regions of β -sheet secondary structure, G: glycosylation sites, []: regions of unobserved electron density, I: intron locations, V: points of major sequence insertion in other vicilin proteins. Shown above the sequence are the labels used to denote the secondary-structural elements in the text. Note that the secondary structure assignments are based on the current unrefined model and thus that the precise start and end points of the strands and helices may be in error by one or two amino acids in some places.

Compared with the 397 residue protein, the 411 residue protein has a five amino-acid insertion after residue 189 and a nine amino-acid insertion after residue 390. The 412 residue protein has a further insertion of one amino acid 5 after residue 100. The chain trace of the electron density map (not shown) is that of the 397 amino-acid protein (termed the \$\rho\$-type polypeptide¹¹) and shows no break or weakening of electron density in the vicinity of residue 189. We thus conclude that the 397 amino-acid protein is overwhelmingly 10 dominant in the crystal. It will be clear to the person skilled in the art that these three genes can be readily interconverted, using presently available techniques. This invention is to be understood to apply to all three forms of the protein.

15 The map shows weak evidence of glycan binding at both known Asn-X-Ser/Thr glycosylation triplets 24. The density is not yet sufficiently clear to provide information about the nature of heterogeneity of the glycans.

Folding topology

unit, which is not structurally

Pigure 2 shows a schematic drawing of the polypeptide. It consists of two structurally-similar units of about 160 amino acids each. These are related by a pseudo-diad axis nearly perpendicular to and intersecting the molecular triad axis. Each unit is itself an κ+β two-domain structure, the first of some 110 residues being a classic viral capsid jelly-roll structure, and the second smaller domain being a cluster of three helices, including a helix-turn-helix motif. A fourth helix in the N-terminal

WO 91/04270 PCT/AU90/00430

associated with the three-helix cluster, forms part of the connection through to the C-terminal unit.

The jelly-roll barrel structure in phaseolin is stripped of nearly all of the elaboration seen in the viral capsid proteins^{25,26}; in this respect it is similar to the barrel structure observed in catabolite gene activator protein (CAP)²⁷. It is convenient to denote the eight strands of the jelly-roll β -barrel as B through I, in analogy with the notation used in the discussion of the viral capsid proteins²⁵. In only two places in phaseolin is there found a loop of structure external to the barrel, between strands F and G of the N-terminal barrel (residues ca 102-108) and between strands E and F of the C-terminal barrel (residues ca 277-286). Each barrel has an A strand reminiscent of the C subunits of the plant virus capsid proteins²⁵, and another β -strand, antiparallel and N-terminal to A, which we label here strand A'. Both barrels have a further strand (which we label J) C-terminal to the barrel, making a total of eleven strands in the β -sheet structure. Strands C of each barrel have a bulge at positions 65-68 and 252-255 respectively.

The helical domains comprise residues ca 156-181 and 340-371, each being a three-helix cluster. These helices bear a striking similarity to a helix-turn-helix motif in Cro, a DNA binding protein²⁸. This will be discussed further below. The occurrence on a single polypeptide of a jelly-roll β -barrel and a helical cluster reminiscent of DNA binding proteins has previously been observed for the CAP protein. However, the

relative position of these two domains in phaseolin and CAP is very different.

The internal sequence repeat 16 observed in phaseolin, jack bean canavalin and pea vicilin is the basis for the structural repeat described here. The sequence similarity in the internal repeat is low (≈15% identity), but the amino-acid alignment corresponds to the structural repeat perfectly in many places and to within a few residues in the worst cases. The domains are remarkably similar; a least-squares fit of the Cα positions in corresponding structural elements of the pair of units yields an r.m.s. deviation of only 2.2Å.

Exon/intron boundaries are the same in phaseolin and conglycinin DNA sequences 29,7,12 . Those five boundaries are, in the first unit, at the DE corner (residue 81), within the J β -strand (144), the H2-H3 corner (171); and in the second unit, the BC corner (248) and the β -> α connection (335). If strand J is considered as a linking element between the β and α structures, then all these boundaries lie at the interconnection of various elements of the secondary structure.

Trimer structure

The six structural $\alpha+\beta$ units which comprise the phaseolin trimer are arranged alternately up and down around the three-fold axis and are nearly coplanar. The trimer is therefore a disc of diameter 90Å and thickness 35Å, as predicted by electron microscopy³⁰ and exhibits approximate 32

point group symmetry. Such an arrangement suggests two types of 'interfaces' between the units, intrachain contacts within one polypeptide, and trimer contacts between the three chains. Each interface is centred around a pseudo-diad relating the two structurally-similar units of the polypeptide. No electron density is visible for the region linking the units (residues 213-219) leaving an apparent ambiguity as to which adjacent pair of units in the trimer is on the one polypeptide chain (see Figure 3). One pair has a distance of 37Å between the Ca positions of residues 212 and 220, and the other has a corresponding distance of 18A. To avoid postulating an extremely extended polypeptide linker, we conclude tentatively that the subunit is most likely formed from the latter pair. (The question of definition of the trimer within the tetramer will be discussed below; for completeness it should be pointed out that it is not possible for the missing polypeptide link to run from an N-terminal unit in one trimer to the C-terminal unit in another as these are separated by \approx 60Å).

The jelly-roll β -barrel has a remarkable capacity to exist in different states of oligomerization^{32,33}. The hexameric pattern observed here with quasi-32 point group symmetry is unlike the packing around the quasi-6-fold axis of the T=3 icosahedral surface lattice²⁶. Furthermore the specific interactions between the barrels seen here are unlike those observed in T=1 capsids²⁵, tumour necrosis factor³⁴ or in the adenovirus hexon³³.

The B-I-D-G face of the two barrels associate with each around

WO 91/04270 - 16 - PCT/AU90/00430

the pseudo-diad in what appears to be a typical example of aligned packing of β -sheets. The two potential N-linked glycosylation sites are both within the C-terminal barrel on strands A and I respectively. The sugar attached to strand I could contact the neighbouring N-terminal barrel.

The helical domains of the subunits are closely associated with each other around the pseudo-diad relating the neighbouring subunits (see Figure 2b). As mentioned above, the helix-turn-helix motifs formed by helices 2 and 3 of each domain are similar to those found in certain DNA-binding proteins³⁵, typified by the Cro protein. A least-squares fit of the $C\alpha$ positions of residues 163-183 and 351-371 of phaseolin to the helix-turn-helix motif formed by residues 16-36 of Cro yields an r.m.s. deviation of 1.9Å and 1.3Å respectively, within the spread determined for these motifs³⁵. The capacity of helix-turn-helix structures to bind DNA is associated with their condensation into dimers with diad symmetry coincident with that of double-stranded DNA, in particular with elements of the diad-related helices positioned 34Å apart and binding to consecutive major grooves of DNA. such 34Å period is evident in the dimerisation of the phaseolin helical domains, nor indeed are the two domains identical. dimensions of that domain pair are more of the order of 18Å (in the trimer, not the polypeptide as we have chosen to define it here, Figure 3), sufficient only to span adjacent major and minor grooves of DNA. All of the DNA-protein structures solved to date which have helix-turn-helix motifs for the DNA binding site exemplify the diad-symmetrical form of binding.

Recent studies^{35,36} of structures in the protein data bank³⁷ have demonstrated that DNA binding protein II³⁸, the ribosomal L7/L12 protein³⁹ and cytochrome C peroxidase⁴⁰ all contain helix-turn-helix motifs. The first two of these bind nucleic acids, whether or not via the helix-turn-helix motif is unknown. However the cytochrome C peroxidase structure embodies the motif semi-internally, making interaction with DNA very unlikely³⁵.

In phaseolin the second helix in the motif (i.e. the third in the helical domain) is exposed to the environment in both structural units on the polypeptide and within the trimer (Figure 3). We know of no evidence suggesting that phaseolin is able to bind DNA, specifically or non-specifically. The translocation of the phaseolin polypeptide from its site of synthesis on membrane-bound polysomes through the endoplasmic reticulum into storage bodies^{41,3} makes such an interaction unlikely. Nevertheless, DNA-binding studies could provide direct evidence for or against a role for storage proteins in the regulation of their own high level of synthesis.

Ligand binding sites

We have previously reported¹⁹ the results of a phosphorus analysis of type II phaseolin crystals which implies that two molecules of phytic acid might be associated with each 50kDa polypeptide. There is no electron-dense feature in the current 3Å map consistent with such binding, though phytate binding to

WO 91/04270 - 18 - PCT/AU90/00430

the flexible ends or linker region of the polypeptide cannot be excluded.

At the interface between the two jelly-roll domains of the subunit involving the sheets B-I-D-G referred to above, there is an intense spherical electron-dense feature lying in a pocket formed by the side chains of residues His 32, Glu 56, Arg 58, Arg 79, Arg 130, Lys 296 and Asp 297. A possible explanation is that it corresponds to phosphate bound either in vivo or during the purification process. A second unexplained, though more diffuse, electron-dense feature occurs within the N-terminal β -barrel and is associated with the side chains of residues Gln 133 and Glu 145.

The tetramer of trimers

The crystallization conditions used here for phaseolin have encouraged the formation of tetrameric 18S particles. The association of trimers into dodecamers under conditions of acid pH is well-characterized 18, and 18S particles so produced have been imaged by electron microscopy 30. The 18S particle observed in the crystal, being formed by four trimers assembled on the faces of a regular tetrahedron, is consistent with the negatively stained e.m. image as judged by the positioning of the solvent channels.

There are two ways of grouping the twelve subunit polypeptide chains in the tetrahedron into trimers. Inspection of the particle shows that in the one association, the intra-trimer WO 91/04270 - 19 - PCT/AU90/00430

polypeptide contacts are extensive (see Figure 3) whereas in the alternate association the subunits are tenuously packed (reminiscent of protein crystal packing). We conclude that the former arrangement is the 7S (150kDa) particle occurring in vivo and observed as a featureless disc by electron microscopy³⁰, and have used this definition of the trimer in the discussion of the preceding sections. The inter-trimer contact in the tetramer occurs at the tetrahedral diad axes. It consists of a symmetry-related pair of interactions, each involving the N-terminal β -barrel of one subunit with the C-terminal β -barrel of a subunit from the neighbouring trimer. The N-terminal strands of polypeptides from neighbouring trimers are also in contact at the tetrahedral diad.

In situ organization

Although no crystallinity of Phaseolus vulgaris seed sections is observable by X-ray diffraction 19 , we cannot rule out a possible link between the curious packing of phaseolin in pseudo-cubic high-salt crystals 19,42 with structures in situ in the seed-storage protein body. (Such a link has been demonstrated for the 11S protein cucurbitin 43). The high-saltcrystals, with pseudo-cubic symmetry P432 and cell dimension a \approx 66Å, can contain only one phaseolin trimer per unit cell. What combination of crystal twinning and/or disorder generates the pseudo-cubic point group is unclear. One possibility emerges from the dodecamer structure observed here. The centre-to-centre distance between the trimers in the tetrahedral 18S particle is \approx 65Å. Packing errors, whereby

trimers are incorporated into the tetrahedral structures without proper cognizance of the top and bottom face of the trimer, could lead to non-closed forms of the tetramer (of trimers) and an average structure in which the 65Å period was associated with a cubic point group. Other explanations include the possibility that the pseudo 32 point group of the trimer is not maintained in high salt, but is distorted into a quasi-cubic structure.

Related Structures

Homology with other vicilins

Sequence alignments imply structural similarity of 7S proteins from common bean, jack bean, soybean and pea seeds 12,15,16. Insertions and deletions in these alignments are, with minor modifications, compatible with the phaseolin structure (see Table 1). For the most part, the phaseolin sequence is shorter than the other sequences, the exception being a five residue insertion around position 350, which may affect the structure of the connection between helices 1 and 2 of the C-terminal structural unit. Significant insertions in the other sequences are found near the N-terminus and at the FG corner (residue 107, Table 1) of the first barrel domain (α '-subunit of β -conglycinin of soybean), in the linker between helices 3 and 4 (residue 188) of the first helical domain (pea vicilin), in the linker (residue 218) between the two $\alpha+\beta$ units (all sequences except phaseolin), and at the EF corner (residue 283) of the second barrel domain (larger inserts for pea proteins

than for soybean). All of these regions are on the surface of the trimer. (The insertion site at residue 218¹⁵ has been placed alternatively at residue 247¹²; we consider that the former leads to the more natural sequence alignment).

A preliminary structure for jack bean canavalin (A.McPherson, personal communication) shows pseudo 32 point group symmetry and a viral capsid domain in each of the two structural units per polypeptide.

Homology with legumins

Based on amino-acid sequence similarity, the basic polypeptide chain of legumins is believed to contain one copy of the repeating structural unit of a vicilin molecule 16, i.e. the $\alpha+\beta$ structure described here. Weak similarity between parts of the acidic chain and the 7S proteins has also been reported, but is less convincing 15 . X-ray diffraction experiments 43 have indicated that the legumin protein cucurbitin has point group symmetry 23, at least at low resolution (ca 20Å). This observation requires that the polypeptide displays an internal repeating structure, which in the 11S particle is a diad, albeit not perpendicular to any three-fold axis. The assembly of the six polypeptides of legumin into the accumulated oligomeric form is believed to proceed via a 7S (trimer) intermediate, the final coalescing of trimers not occurring until cleavage of the polypeptides into the basic and acidic chains 44. If the trimer form is indeed similar to the vicilin 7S molecules, with pseudo point group 32, then a rearrangement

of the subunits within the trimer must accompany the formation of the llS particle, in order to satisfy the resulting cubic arrangement of diads and triads.

Novel phaseolins

Some attempt has previously been made to increase the sulphur content of phaseolin by the insertion of a 45 base-pair synthetic duplex, rich in methionine-codons, at the Xba I site in the third exon of the s-phaseolin gene. Transgenic tobacco plants containing normal or modified phaseolin genes were then monitored for the production and deposition of phaseolin. Whereas in both cases phaseolin expression was achieved, deposition of the modified protein in the storage bodies did not occur, suggesting prior degradation 45. Using the three-dimensional structure, we are now able to identify the Xba I site (after residue 165, Table 1) as being internal to helix 2 (i.e. the first helix in the helix-turn-helix motif) and hence part of a major structural element of the phaseolin trimer. We therefore predict that an

inclusion of fifteen residues at this site could distort the 20 structure at the tertiary and/or quaternary level, making the modified protein more susceptible to degradation.

Conclusions

We have now confirmed the internal repeat observed in the sequence of phaseolin at a structural level; this repeat manifests itself as a pair of \$\alpha + \beta\$ units forming the 50kDa subunit. The high sequence similarity to other 7S storage proteins suggests a common structure; indeed a preliminary X-ray structure for canavalin, the 7S protein of the jack bean, indicates a hexameric arrangement of \$\beta\$-barrels 30 as described here (A. McPherson, personal communication).

The structure presented here identifies surface regions of the molecule, which represent candidate sites for genetically-engineered insertions into the sequence.

The invention will now be illustrated by way of reference only to the following non-limiting examples. The references to amino acid sequence numbering are as in Table 1.

In these examples, site directed mutagenesis is used 5 to introduce desired mutations at defined sites in known fragments of wild type phaseolin cDNA.

Mutations are introduced by known methods, such as those described by Kunkel (46), into restriction fragments which include the segment of DNA encoding the locus for the 10 desired mutation. The resulting DNA is used to transfect a host, such as E.coli, and single stranded DNA prepared from The presence of the desired mutation is confirmed by complete sequencing of the same restriction fragment, for example using the method of Sanger et al. (47). The double 15 stranded replicative form of DNAs of proven mutants is isolated, and the mutant restriction fragments isolated by agarose electrophoresis (48). These fragments are then used to replace the corresponding fragment of wild type DNA in an expression vector. All the recombinant methods used are as 20 described by Sambrook et al. (48). Other suitable methods for these procedures would readily occur to the person skilled in the art.

Example 1 - Engineering of High Methionine Phaseolin Mutations The two sequences selected as targets for

25 engineering of high-methionine phaseolins are "ILVLV" in region E between amino acids 61 and 120, Table 1 and "IVILV" in region D between amino acids 241 and 300, Table 1, which both correspond to hydrophobic domains, ie. regions of internal / structure. Each of these sequences is mutated to 30 code for methionine pockets (MMMMM) by iterated cycles of oligonucleotide site-directed mutagenesis. An intron-less /-phaseolin minigene is mutated; this minigene, designated / wti-, has recently been shown to direct efficient expression of phaseolin protein in transgenic tobacco seeds (Bustos et 35 al., 1990; (49)). The advantages of using the minigene

instead of phaseolin genomic DNA fragments derive from the absence of intervening sequences. This facilitates the design of gene constructions and permutations of DNA fragments to combine different mutations. Due to the large number of 5 individual nucleotides that need to be mutated over a span of 15 or 18 nucelotides, a strategy involving multiple rounds of mutagenesis is preferable to one that would attempt to produce all changes at once. This has the added advantage of generating intermediates with fewer than five new methionines, 10 which may be useful when assessing the effects of individual amino acid changes on the structure and in vivo stability of the protein. The detailed mutagenesis strategies are as follows:

"ILVLV" site:

- A 381 bp EcoRI-PstI restriction fragment from clone βwtⁱ⁻(Bustos et al., 1990) is subcloned into the phagemid vector pBSKS+ (Stratagene) and the resulting clone is used to produce a U-containing single stranded DNA template. Three different synthetic single-stranded oligonucleotide DNA 20 molecules (shown below as oligos I to III) are utilized to
- 20 molecules (shown below as oligos I to III) are utilized to mutagenize the wt sequence by the method of Kunkel (46). The individual base substitutions are indicated in boldface. Screening of mutated clones is performed directly by sequencing with an oligonucleotide primer designed to

25 hybridize 35 nucleotides upstream of the target sequences.

wt ... ggg agc gcc ATA CTC GTC TTG GTG aaa cct gat ...
oligo I 5'agc gcc ATG ATG GTC TTG ATG aaa cct 3'
oligo II 5'gcc ATG ATG ATG ATG ATG aaa cct 3'
final 81gly ser ala Met Met Met Met Met lys pro asp⁹¹
... ggg agc gcc ATG ATG ATG ATG ATG aaa cct gat ...

After each round of mutagenesis has been completed, the new EcoRI-PstI DNA fragments are replaced into the β wtⁱ⁻gene to yield modified phseolin genes coding for two, three and five new methionine residues.

5 "IVILV" site"

A 2.0 kbp XbaI-BamHI restriction fragment from clone but i- (Bustos et al., 1990) is subcloned into the phagemid vector pBSKS+ (Stratagene) and the resulting clone used to produce a U-containing single-stranded DNA template. In a 10 manner analogous to that employed at the ILVLV site, three synthetic oligonucleotides (oligos IV to VI, shown below) are used to mutagenize the wt sequence using the same method. As for the other site, each oligo is designed to mutate two or three closely spaced nucleotides, and all oligos result in at 15 least one new methionine codon.

wt ...tct aag gcc ATT GTT ATA CTA GTG gtt aat gaa gga ...
oligo IV 5'aag gcc ATG ATG ATA CTA GTG 3'
oligo V 5'TG ATA CTG ATG gtt aat 3'
20 oligo VI final 258 ser lys ala Met Met Met Met Met val asn glu gly 269
...tct aag gcc ATG ATG ATG ATG ATG gtt aat gaa gga ...

As for the ILVLV site, the sequences at and around the mutated sites are verified using a sequencing primer that 25 hybridizes near the site. After mutagenesis the XbaI-BamHI fragments are replaced into \(\beta \text{wt}^{\dagger} \) or into the high-methionine mutants modified at the ILVLV site. A maximum of ten new methionine residues result from the combination of mutations at both sites.

30 All mutated phaseolin genes are subsequently subcloned into the binary vector pBIN19 and transferred into the genome of tobacco by A. tumefaciens-mediated transformation.

Example 2 - Model Building of High-Methionine Mutant Phaseolin The structure of the high-methionine mutant phaseolin can be investigated by model-building as follows. An interactive molecular-graphics computer program (QUANTA,

- 5 Polygen Corporation) was used to model the replacement of residues 84 to 88 and 261 to 265 by methionine. The energy-refinement computer-program XPLOR (Harvard University) was then used to refine the atomic coordinates of the mutant structure to ensure that favourable stereochemistry is
- 10 achieved, keeping the remainder of the protein as close as possible to the native structure. The results of the modelling are shown in Figures 4 and 5; there are no significant difference in energy between the native and mutant structures (native: -11529 Kcal/mol, mutant: -11677 Kcal/mol)
- 15 and no disruption to the tertiary or quaternary structure is predicted.

Example 3

The environment of the following residues in the phaseolin structure indicates that they can be altered to 20 Methionine without prejudice to the three-dimensional structure of the protein:

Leu 65, Leu 76, Phe 252, Leu 264, Ile 177, Leu 181.

Example 4

Mutation of Isoleucine 105 to Asparagine introduces 25 an N-linked glycosylation site at that position. Sugar attached at that site may be accommodated on the surface of the phaseolin trimer.

Example 5

Elimination of the loop of structure between beta 30 strands E and F of the C-terminal structural unit may be accomplished by deleting residues numbered 278 to 287 and

10

15

replacing them with a linker of two glycine residues. This increases the stability of phaseolin to enzymes with trypsin-like specificity.

In general, the selection of sites for mutagenesis 5 may be influenced by the accessibility of the target site to restriction endonucleases. The criteria for assessing whether the desired mutation has been achieved will depend on the nature of the mutation attempted, but include;

- a) sequencing of the DNA in the construct;
- b) analysis of the product protein for presence or absence of the desired property, eg. by amino acid analysis or susceptibility to enzymes;
- c) retention of tertiary or quaternary structure;
- d) cross-reaction with antibody directed against the native protein; and
- e) successful expression in vivo.

For example, if the mutation is to substitute methionine for another amino acid, the presence of one or two met residues could be detected by cyanogen bromide cleavage;

20 the presence of about 10 met residues could be readily assayed by amino acid analysis. Retention of three dimensional structure (tertiary or quaternary) can be assessed in advance by model building, and tested in the protein actually produced

25 analyses such as molecular weight, solubility, and circular dichroism spectral studies. Other suitable methods will be known to those skilled in the art.

by success in expression in vivo, and by various physical

Although the invention has been illustrated with reference to phaseolin, sequence homologies indicate that 30 similar results may be expected with related proteins, such as the homologous protein from pea, and to some extent with legumins as implied by the homology described in reference 16.

References cited herein are identified in full on the following pages.

It will be clearly understood that the invention in its general aspects is not limited to the specific details referred to hereinabove.

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WO 91/04270

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CLAIMS:

- l. A mutein which is a variant of a naturally-occurring legume seed storage protein, wherein said mutein has a modified primary structure relative to said legume storage protein, but retains the tertiary and quaternary structure of said legume storage protein.
- 2. A plant 7S or 11S storage protein modified at a specific amino acid residue or a specific region of its amino acid sequence, wherein the tertiary and quarternary structure of the naturally occurring storage protein is retained.
- 3. A storage protein according to Claim 1 or Claim 2, wherein the modification is selected from the group consisting of:
 - (a) introduction of one or more point mutations;
 - (b) deletion of one or more defined sequences of amino acids;
- (c) insertion of one or more defined sequences of amino acids;
- (d) introduction of one or more glycosylation sites; and
 - (e) introduction of one or more disulphide bonds.
- 4. A plant storage protein according to Claim 3, wherein the modification is selected from the group consisting of:
 - (a) introduction of N-linked glycosylation sites;
- (b) substitution of internal amino acids by methionine;
 - (c) truncation of protease-labile loops; and
 - (d) introduction of protease-labile loops.
- 5. A protein according to any one of Claims 1 to 5 which is a vicilin or a legumin.
- 6. A protein according to Claim 5 which is a phaseolin.
- 7. A DNA molecule whose sequence encodes a storage protein as defined in any one of Claims 1 to 6.

- 8. A DNA molecule according to Claim 7, whose sequence encodes a protein having the properties of a plant 7S or 1lS storage protein, and also encodes one or more of the modifications set out above.
- 9. A DNA molecule according to Claim 8 wherein the protein is a vicilin or a legumin.
- 10. A DNA molecule according to Claim 9 wherein the protein is phaseolin.
- 11. An autonomous unit of DNA replication in vivo or in vitro selected from the group consisting of plasmids, cosmids, expression vectors, microorganisms, viruses and chromosomes, said autonomous unit comprising a DNA molecule according to any one of Claims 7 to 10.
- 12. A autonomous unit of DNA replication according to Claim ll which is Agrobacterium tumefaciens.
- 13. A autonomous unit of DNA replication according to Claim 11 which is a plant virus.
- 14. A transgenic plant or part thereof comprising a DNA sequence as defined in any one of Claims 7 to 10.
- 15. A seed of a transgenic plant according to Claim 14.
- 16. A product obtained from a plant according to Claim
- 14.

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3.50
                                                                 23.77
                                                   3.50
              2.38 -16.30 22.82 : ASP CG
                                              11
ASP CB
         11
                                                           4.54
                                                                23.28
                            24.98 : ASP OD2 11
                                                   4.54
ASP OD1
         11
              3.32 -16.13
                                                   4.63
                                                          4.63 21.67
                                              11
                            21.93 : ASP 0
              3.49 -18.33
ASP C
         11
                                                   3.07
                                                          3.07 21.63
                            20.49 : ASP CA
                                              11
              2.22 -16.70
ASP N
         11
                                                          2.97 22.44
                                              12
                                                   2.97
              2.64 -19.23
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ASN N
         12
                                                          2.75 23.84
                                                   2.75
              2.52 -21.35
                            23.74 : ASN CG
                                             12
ASN CB
         12
                                                          3.03 22.85
                            24.91 : ASN ND2 12
                                                   3.03
ASN OD1 12
              2.74 -23.40
                                                          1.03 21.53
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                            21.29 : ASN 0
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ASN C
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              2.17 -21.25
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                                                          3.98 19.67
              2.61 -21.42
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         13
PRO N
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1.15 19.00
1.52 19.91
2.02 20.44
                                                 2.73
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PRO CA
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                            18.43 : PRO C
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         13
PRO CG
                            18.17 : PHE N
                                                   1.52
                                              14
              0.33 -23.52
PRO 0 . 13
                                              14
                                                   2.02
                            19.99 : PHE CB
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                            19.80 : PHE CD1 14 3.66
                                                         3.66 18.58
              3.38 -26.29
PHE CG
         14
                            20.43 : PHE CE1 14 4.86
                                                         4.86 18.03
             4.30 -25.52
PHE CD2 14
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                                                         5.78 18.66
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                            20.96 : PHE 0
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PHE C
         14
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             -0.48 -24.55
TYR N
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TYR CB
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TYR CD1 15 -2.89 -24.76
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                                                                 26.52
TYR CD2 15 -2.24 -22.53
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                            26.94 : TYR OH
                                             15
                                                 -4.88
TYR CZ
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                                                         -2.79 22.14
                                              15
                                                 -2.79
                            22.24 : TYR 0
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TYR C
                                                         -5.13 21.61
                                                 -5.13
         16 -3.79 -24.86
                            21.99 : PHE CA
                                              16
PHE N
                                              16 -5.13
                                                         -5.13 19.4C
         16 -5.79 -25.46
                            20.73 : PHE CG
PHE CB
                                                        -3.89 19.22
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PHE CD1 16 -5.78 -24.67
                            17.23 : PHE CE2 16 -3.26 -3.26 18.04
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PHE CEl 16
                                             16 -5.97 -5.97 22.86
             -3.90 -25.08
                            17.06 : PHE C
PHE CZ
         16
                            23.52 : ASN N 17 -6.17 -6.17 23.16
24.39 : ASN CB 17 -6.43 -6.43 24.56
25.93 : ASN OD1 17 -6.11 -6.11 26.28
26.78 : ASN C 17 -8.22 -8.22 24.31
         16
             -6.47 -25.11
PHE O
             -6.76 -22.52
ASN CA
         17
             -6.74 -20.63
ASN CG
         17
                            26.78 : ASN C
ASN ND2 17
            -7.57 -21.19
                                                         -8.90 25.22
                                              18 -8.90
                            23.39 : SER N
         17 -8.80 -22.09
ASN O
                                             18 -10.82 -10.82 26.02
         18 -10.32 -23.45
                            25.06 : SER CB
SER CA
                                             18 -11.09 -11.09 25.21
                            27.25 : SER C
         18 -10.32 -23.95
SER OG
                                             19 -10.50 -10.50 25.59
                            24.86 : ASP N
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SER O
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                            25.67 : ASP CB
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ASP CA
            -9.66 -18.65 27.12 : ASP OD1 19 -8.90 -8.90 26.16
ASP CG
         19
                                             19 -11.36 -11.36
                                                                24.38
                            28.26 : ASP C
            -9.28 -18.47
ASP OD2
         19
                                                                 23.44
                                              20 -10.48 -10.48
                            24.14 : ASN N
         19 -12.23 -18.33
ASP O
                                                                 21.92
                            22.13 : ASN CB 20 -9.90 -9.90
21.99 : ASN OD1 20 -8.00 -8.00
                                              20 -9.90 -9.90
         20 -10.77 -18.92
ASN CA
                                                                 21.36
         20 -8.44 -18.06
ASN CG
                                              20 -10.63 -10.63
                                                                 21.00
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SER OG
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SER O
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TRP CA
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TRP CG
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TRP CE2
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TRP CZ2
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TRP 0
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ASN CG
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                            15.85 : ASN C
ASN ND2 23 -14.30 -20.93
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THR CA
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III 1.2.
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 LYS C
 ASN N
 ASN CB
 ASN OD1
 ASN C
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 GLN NE2 29 -33.66 -26.09 23.97 : GLN C
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 TYR CG
 TYR CE1
 TYR CE2
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 TYR .O
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GLY O
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 HIS CG
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HIS O
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ILE CG2 33 -23.41 -31.12 17.27 : ILE CG1 33 -21.57 -21.57 16.25 ILE CD1 33 -20.20 -30.72 15.72 : ILE C 33 -20.51 -20.51 18.49 ILE O 33 -20.99 -27.83 18.00 : ARG N 34 -19.24 -19.24 18.89
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ARG NE
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VAL CG2 35 -17.30 -28.05
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GLN OE1 37 -7.42 -20.76 16.96 : GLN NE2 37 -6.95 -6.95 14.99
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GLN C
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 ARG CB
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SER CB
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LEU CD1
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 ARG N
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 ARG NH2
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 ARG O
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 LEU CD2
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 VAL C
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 GLU N
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 GLU CB
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GLU OE2
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SER OG
         59 -25.92 -36.63 23.38 : SER C
                                             59 -26.21 -26.21 26.12
         59 -25.56 -35.97 26.72 : LYS N
SER O .
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LYS CA
         60 -27.95 -35.01 27.84 : LYS CB
                                             60 -29.05 -29.05 28.11
                           27.99 : LYS CD
LYS CG
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                           27.77 : LYS O
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PRO CG
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PRO O
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GLU CA
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                                            62 -35.03 -35.03
                           29.02 : GLU OE2
GLU OE1
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                                                               29,49
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                           25.37 : GLU O
                                             62 -33.08 -33.08
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GLU C
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THR N
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                                                               23.73
THR CB
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                           23.71 : THR C
                                            63 -30.77 -30.77
                                                               22.14
THR CG2
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THR 0
         63 -30.02 -39.56
         64 -30.75 -38.64 19.68 : LEU CB 64 -31.87 -31.87 18.98 64 -31.85 -39.57 17.47 : LEU CD1 64 -31.67 -31.67 17.07
LEU CA
LEU CG
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LEU CD2
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                             18.89 : LEU N
 LEU O
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                                                                 18.08
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 LEU CG
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 LEU CD2
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 LEU O
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 LEU CD2
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                             14.28 : LEU C
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                                                                 12.65
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                                     PRO CG
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 GLN NE2
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GLU CD
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GLU OE2
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LEU CD2
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VAL CA
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VAL O
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                            25.58 : ARG CD
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                            25.50 : ARG CZ
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ARG NE
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                           25.61 : ARG NH2
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        79 -13.07 -33.09
ARG NH1
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顶_1.6.

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 SER CB
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                             29.61 : SER OG
                                                80 -17.56 -17.56
                                                                   30.62
 SER C
           80 -19.07 -41.27
                              28.53 : SER 0
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                                                81 -19.64 -19.64 28.06
 GLY N
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 GLY C
                                                81 -21.73 -21.73 28.31
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 SER N
           82 -23.92 -43.63 26.88 : SER OG
                                               82 -23.45 -23.45 26.23
 SER CB
           82 -23.01 -44.67
 SER C
                             24.89 : SER 0
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           83 -23.96 -44.07 24.15 : ALA CA
                                               83 -23.96 -23.96 22.68
 ALA N
           83 -22.71 -43.47 22.06 : ALA C
                                               83 -24.11 -24.11 21.88
 ALA CB
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84 -26.99 -26.99 20.33
84 -27.19 -27.19 21.63
84 -25.32 -25.32 18.87
85 -24.51 -24.51 17.94
85 -22.90 -22.90 16.51
           83 -23.33 -46.28 21.95 : ILE N
 ALA O
           84 -25.51 -46.45 20.19 : ILE CB
 ILE CA
          84 -27.43 -47.70 19.14 : ILE CG1
84 -28.67 -47.63 22.03 : ILE C
 ILE CG2
 ILE CD1
           84 -25.98 -44.71 18.65 : LEU N
 ILE O
           85 -24.36 -45.46 16.70 : LEU CB
 LEU CA
           85 -22.27 -44.83 15.24 : LEU CD1 85 -22.67 -22.67 14.86
 LEU CG
          85 -20.78'-45.01 15.45 : LEU C
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 LEU CD2
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 LEU O
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          86 -26.00 -46.71 13.56 : VAL CB
 VAL CA
 VAL CG1 86 -28.28 -46.04 14.42 : VAL CG2 86 -28.15 -28.15 12.19
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          86 -25.55 -46.05 12.27 : VAL 0
 VAL C
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87 -22.11 -22.11 10.54
87 -21.85 -21.85 11.28
 LEU N
          87 -24.88 -46.77 11.38 : LEU CA
 LEU CB
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 LEU CD1 87 -20.93 -47.07
                              9.70 : LEU CD2
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          87 -25.66 -46.73
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 LEU C
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VAL N
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VAL CB
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VAL CG2 88 -29.12 -45.33
                              8.76 : VAL C
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VAL O
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LYS CG
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LYS C
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PRO CA
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ASP OD2 91 -25.10 -52.76
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ARG NH2
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GLU CA
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115.1.7.
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 GLU CG
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 GLU OE1 95 -20.79 -51.95
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 TYR CB
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TYR CD2
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PHE CD1
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PHE CE1
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LEU CB
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        104 -13.35 -54.64
PRO CB
                                            104 -16.50 -16.50
                                                                27.93
                            27.65 : PRO O
         104 -15.33 -54.33
PRO C
                                            105 -16.08 -16.08 25.86
                            26.75 : ILE CA
         105 -15.07 -55.33
ILE N
                            26.63 : ILE CG2 105 -17.34 -17.34 27.98
        105 -16.66 -57.27
ILE CB
                            25.68 : ILE CD1 105 -17.03 -17.03 24.74
ILE CG1 105 -17.66 -58.03
                                             105 -18.41 -18.41 25.61
                            25.35 : ILE 0
         105 -17.21 -55.05
 ILE C
                                            106 -17.58 -17.58 24.07
                            24.75': PHE CA
         106 -16.74 -53.92
PHE N
                                            106 -19.83 -19.83 25.17
                            25.06 : PHE CG
PHE CB 106 -18.48 -52.14
                            24.14 : PHE CD2 106 -20.57 -20.57 26.33
PHE CD1 106 -20.28 -53.69
                            24.27 : PHE CE2 106 -21.75 -21.75 26.45
PHE CE1 106 -21.47 -54.41
                                             106 -16.93 -16.93 23.13
                            25.44 : PHE C
        106 -22.21 -54.28
PHE CZ
                                             107 -15.73 -15.73 23.38
         106 -17.52 -51.66
                            22.05 : SER N
PHE O
                                            107 -15.18 -15.18 20.98
                            22.50 : SER CB
        107 -15.09 -50.38
 SER CA
                                             107 -15.70 -15.70
                            20.37 : SER C
        107 -14.04 -50.06
SER OG
                                             108 -14.70 -14.70 22.76
                            22.83 : ASP N
         107 -16.90 -48.77
SER O
                                            108 -14.05 -14.05 24.02
                            22.94 : ASP CB
        108 -14.95 -46.76
ASP CA
                            23.80 : ASP OD1 108 -11.87 -11.87 24.62
        108 -12.55 -46.26
ASP CG
                                            108 -14.74 -14.74 21.65
                            22.86 : ASP C
ASP OD2 108 -12.00 -46.87
                                            109 -14.51 -14.51 20.54
        108 -14.81 -44.84 21.62 : HIS N
ASP 0
```

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顶、1.8.
```

HIS CA 109 -14.47 -45.96 19.31 : HIS CB 109 -13.14 -13.14 18.95 HIS CG 109 -12.21 -46.61 19.00 : HIS CD2 109 -11.61 -11.61 17.95 HIS ND1 109 -11.80 -47.13 20.13 : HIS CE1 109 -10.92 -10.92 19.84 HIS NE2 109 -10.81 -48.11 18.52 : HIS C 109 -14.94 -14.94 18.07 HIS O 109 -15.10 -47.83 18.08 : GLN N 110 -15.06 -15.06 16.97 GLN CA 15.78 : GLN CB 110 -17.11 -17.11 110 -15.62 -46.48 16.04 14.97 : GLN CD 110 -17.02 -17.02 GLN CG 110 -17.80 -47.48 14.40 GLN OE1 110 -16.83 -48.73 13.20 : GLN NE2 110 -16.49 -16.49 15.14 GLN C 110 -15.33 -45.49 14.67 : GLN 0 110 -15.29 -15.29 14.92 111 -15.06 -45.99 13.48 : LYS CA 111 -14.74 -14.74 LYS N 12.34 LYS CB 111 -13.62 -45.88 11.64 : LYS CG 111 -13.16 -13.16 10.33 9.49 : LYS CE 10.35 LYS CD 111 -12.32 -46.31 111 -11.20 -11.20 111 -9.93 -47.28 9.70 : LYS C 111 -15.99 -15.99 11.48 LYS NZ 111 -16.47 -46.07 10.95 : ILE N 112 -16.58 -16.58 11.34 LYS O 10.51 : ILE CB 112 -18.60 -18.60 ILE CA 112 -17.76 -43.75 11.06 10.27 : ILE CG1 112 -18.83 -18.83 13.03 : ILE C 112 -17.18 -17.18 ILE CG2 112 -19.90 -42.58 12.53 ILE CD1 112 -19.66 -41.59 9.13 112 -16.49 -42.41 9.10 : PRO N 7.98 113 -17.31 -17.31 ILE 0 113 -18.03 -45.26 7.79 : PRO CA 113 -16.49 -16.49 6.82 PRO CD 113 -16.58 -44.96 6.01 : PRO CG 113 -17.03 -17.03 PRO CB 6.98 113 -16.94 -42.47 6.08 : PRO 0 113 -18.13 -18.13 6.09 PRO C 114 -16.15 -41.73 5.35 : ALA CA 114 -16.62 -16.62 ALA N 4.74 3.92 ALA CB 114 -15.47 -39.96 3.92 : ALA C 114 -17.91 -17.91 2.70 : GLY N ALA O 114 -17.91 -40.47 115 -19.07 -19.07 4.50 115 -20.23 -39.80 3.73 : GLY C 115 -21.33 -21.33 4.04 GLY CA 3.36 : THR N 115 -22.33 -40.62 116 -21.16 -21.16 5.00 GLY 0 THR CA 116 -22.15 -42.66 5.54 : THR CB 116 -21.62 -21.62 6.54 6.13 : THR CG2 116 -22.37 -22.37 THR OG1 116 -20.35 -44.09 6.51 THR C 116 -23.11 -41.88 6.39 : THR 0 116 -22.63 -22.63 7.11 6.31 : ILE CA 117 -25.35 -25.35 7.14 ILE N 117 -24.40 -42.15 6.42 : ILE CG2 117 -27.84 -27.84 117 -26.70 -41.56 7.40 ILE CB ILE CG1 117 -26.83 -40.39 5.47 : ILE CD1 117 -28.22 -28.22 4.94 117 -25.33 -42.10 8.52 : ILE O 117 -25.25 -25.25 8.59 ILE C 118 -25.40 -41.42 9.65 : PHE CA 118 -25.34 -25.34 10.93 PHE N PHE CB 118 -23.88 -42.14 11.46 : PHE CG 118 -23.14 -23.14 11.78 118 -23.88 -42.14 11.46 : PRE CG 116 -23.14 -23.14 11.76

118 -23.21 -40.33 13.06 : PHE CD2 118 -22.47 -22.47 10.81

118 -22.61 -39.14 13.35 : PHE CE2 118 -21.87 -21.87 11.12

118 -21.94 -38:47 12.38 : PHE C 118 -26.24 -26.24 11.90

118 -26.40 -40.18 11.74 : TYR N 119 -26.89 -26.89 12.87

119 -27.52 -41.17 13.89 : TYR CB 119 -29.07 -29.07 13.80

119 -29.81 -42.53 13.49 : TYR CD1 119 -29.75 -29.75 12.23 PHE CD1 118 -23.21 -40.33 PHE CE1 118 -22.61 -39.14 PHE CZ 118 -21.94 -38:47 PHE 0 TYR CA TYR CG TYR CE1 119 -30.40 -44.23 12.00 : TYR CD2 119 -30.50 -30.50 14.50 TYR CE2 119 -31.15 -44.38 14.27 : TYR CZ 119 -31.08 -31.08 13.00 119 -27.01 -27.01 15.20 TYR OH 119 -31.57 -46.13 12.70 : TYR C 119 -26.45 -42.78 15.23 : LEU N 120 -27.11 -27.11 16.31 TYR O LEU CA 120 -26.42 -41.44 17.53 : LEU CB 120 -25.31 -25.31 17.83 LEU CG 120 -23.86 -40.75 17.90 : LEU CD1 120 -23.09 -23.09 17.72 LEU CG LEU CG 120 -23.86 -40.75 17.90 : LEU CD1 120 -23.09 -23.09 17.72 LEU CD2 120 -23.50 -41.32 19.23 : LEU C 120 -27.47 -27.47 18.62 LEU O 120 -28.22 -40.39 18.55 : VAL N 121 -27.70 -27.70 19.56 VAL CA 121 -28.66 -41.97 20.61 : VAL CB 121 -29.94 -29.94 20.60 VAL CG1 121 -30.11 -43.46 19.21 : VAL CG2 121 -29.89 -29.89 21.59 VAL C 121 -27.88 -42.08 21.90 : VAL O 121 -26.85 -26.85 21.88 ASN N 122 -28.22 -41.40 23.00 : ASN CA 122 -27.49 -27.49 24.27 ASN CB 122 -27.36 -40.18 25.06 : ASN CG 122 -26.75 -26.75 26.48 ASN OD1 122 -26.35 -41.42 26.91 : ASN ND2 122 -26.65 -26.65 27.33 122 -28.42 -42.42 25.04 : ASN 0 122 -29.52 -29.52 25.43 ASN C 123 -27.98 -43.66 25.22 : ARG CA 123 -28.84 -28.84 25.72 ARG N ARG CB 123 -28.18 -45.97 25.51 : ARG CG 123 -26.78 -26.78 26.17 ARG CD 123 -26.34 -46.96 27.34 : ARG NE 123 -26.83 -26.83 28.73

顶. 1.9.

```
ARG CZ 123 -27.92 -47.53 29.20 : ARG NH1 123 -28.26 -28.26 30.51
                                                123 -29.16 -29.16
                                                                      27.17
ARG NH2 123 -28.69 -48.33 28.35 : ARG C
                                                124 -28.41 -28.41
                                                                      27.89
         123 -29.99 -45.29 27.68 : ASP N
ARG O
        124 -28.41 -43.82 29.32 : ASP CB 124 -27.00 -27.00
                                                                      29.66
ASP CA
        124 -26.82 -43.92 31.10 : ASP OD1 124 -27.09 -27.09
                                                                      31.98
ASP CG
                                                124 -29.33 -29.33
                                                                      29.92
ASP OD2 124 -26.50 -45.09 31.31 : ASP C
                                                125 -30.06 -30.06
                                                                      31.04
         124 -29.39 -41.67 29.34 : PRO N
ASP 0
         125 -30.08 -44.21 31.82 : PRO CA 125 -31.11 -31.11
                                                                      31.51
PRO CD
         125 -32.18 -43.01 31.95 : PRO CG 125 -31.31 -31.31
                                                                      32.70
PRO CB
                                                125 -31.38 -31.38
                                                                      33.15
         125 -30.60 -41.19 32.61 : PRO O
PRO C
                                               126 -28.78 -28.78
         126 -29.29 -41.29
                              32.93 : LYS CA
LYS N
                                                                      36.08
                                               126 -27.64 -27.64
         126 -28.84 -41.09
                             35.28 : LYS CG
LYS CB
                                                                      36.36
                             35.39 : LYS CE
                                               126 -25.85 -25.85
         126 -26.81 -42.73
LYS CD
                                                                      33.54
                                                126 -27.42 -27.42
         126 -25.25 -42.56
                             37.35 : LYS C
LYS NZ
                                                                      33.07
                                                127 -26.40 -26.40
         126 -27.33 -38.50
                             33.61 : GLU N
LYS O
                                               127 -24.13 -24.13
                                                                      32.94
                             32.71 : GLU CB
         127 -25.14 -39.81
GLU CA
                                                                      35.61
                                               127 -23.80 -23.80
         127 -23.20 -40.68
                             34.17 : GLU CD
GLU CG
GLU OE1 127 -24.84 -39.90 35.86 : GLU OE2 127 -23.27 -23.27
                                                                      36.56
                                                127 -25.88 -25.88
                                                                     30.39
         127 -25.15 -39.17 31.28 : GLU 0
GLU C
                                                128 -24.42 -24.42
         128 -24.51 -38.01 30.97 : ASP CA
ASP N
                                               128 -24.72 -24.72
                                                                      30.18
ASP OD1 128 -24.75 -33.82 29.78 : ASP OD2 128 -25.42 -25.42 31.15
ASP C 128 -23.55 -38.30 28.66 : ASP O 128 -22.91 -22.91 29.09
        128 -23.82 -36.04
                             29.56 : ASP CG
         129 -23.48 -37.96 27.37 : LEU CA 129 -22.63 -22.63
                                                                      26.39
LEU N
         129 -23.33 -38.90 25.07 : LEU CG 129 -22.98 -22.98
LEU CB
LEU CD1 129 -23.13 -39.52 22.75 : LEU CD2 129 -21.59 -21.59
                                                                      24.30
                                                                      25.88
                                                129 -21.95 -21.95
         129 -21.54 -37.63 26.09 : LEU O
LEU C
         130 -20.24 -37.98 26.09 : ARG CA 130 -19.26 -19.26
                                                                      25.66
ARG CB 130 -18.44 -36.57 26.87 : ARG CG 130 -19.22 -19.22

ARG CD 130 -18.43 -34.73 28.70 : ARG NE 130 -17.26 -17.26

ARG CZ 130 -16.05 -34.80 29.39 : ARG NH1 130 -15.10 -15.10

ARG NH2 130 -15.64 -33.58 28.94 : ARG C 130 -18.36 -18.36

ARG O 130 -17.39 -38.20 24.75 : ILE N 131 -18.52 -18.52
ARG N
                                                                      27.86
                                                                      29.95
                                                                      24.52
                                                                     23.24
         131 -17.68 -37.73 22.17 : ILE CB 131 -18.61 -18.61
                                                                     20.99
ILE CA
ILE CG2 131 -17.86 -38.40 19.73 : ILE CG1 131 -19.50 -19.50 21.44
                                                                      21.79
ILE CD1 131 -20.52 -39.68 20.45 : ILE C
                                                131 -16.58 -16.58
         131 -16.80 -35.58 21.98 : ILE N
                                                132 -15.42 -15.42 21.31
ILE 0
ILE CA 132 -14.31 -36.36 20.82 : ILE CB 132 -13.06 -13.06
                                                                     21.79
ILE CG2 132 -12.38 -37.80 21.79 : ILE CG1 132 -11.95 -11.95 21.26
THE CD1 132 -12.16 -34.09 21.44 : THE C 132 -14.02 -14.02 19.44

THE O 132 -14.06 -38.21 19.37 : GLN N 133 -13.77 -13.77 18.28

GLN CA 133 -13.61 -37.13 17.05 : GLN CB 133 -14.76 -14.76 16.13

GLN CG 133 -16.08 -37.06 16.81 : GLN CD 133 -17.25 -17.25 15.86
GLN 0E1 133 -17.14 -37.00 14.66 : GLN NE2 133 -18.47 -18.47
                                                                     16.28
                                                 133 -12.25 -12.25
         133 -12.46 -36.54 16.31 : GLN 0
GLN C
         134 -11.69 -37.35 15.61 : LEU CA 134 -10.65 -10.65
                                                                      14.76
LEU N
              -9.42 -37.67 14.78 : LEU CG 134 -8.39 -8.39
                                                                      13.77
LEU CB
         134
LEU CD1 134 -7.62 -36.10 14.11 : LEU CD2 134 -7.47 -7.47
                                                                      13.73
                                                 134 -11.86 -11.86
                                                                      13.10
         134 -11.35 -36.91 13.42 : LEU O
LEU C
         135 -11.48 -35.87 12.63 : ALA CA 135 -12.19 -12.19
                                                                      11.40
ALA N
                                                                     10.34
         135 -13.27 -34.89 11.39 : ALA C
                                                 135 -11.15 -11.15
ALA CB
                                                                       9.19
                                                 136 -11.13 -11.13
         135 -10.30 -34.77 10.58 : MET N
ALA O
                                                     -9.42 -9.42
                                                                       7.85
                               8.14 : MET CB
                                                 136
         136 -10.17 -36.01
MET CA
                                                     -8.72 -8.72
                                                                       9.74
                                                136
                                9.12 : MET SD
         136 -8.72 -37.84
MET CG
                                                 136 -11.01 -11.01
                                                                       6.95
         136 -10.20 -39.92 10.67 : MET C
MET CE
                                                 137 -11.22 -11.22
                                6.36 : PRO N
         136 -11.64 -36.43
MET O
                                                                       5.49
                                                137 -12.14 -12.14
                                7.14 : PRO CA
         137 -10.68 -33.11
PRO CD
                                                                       7.02
                                                137 -11.86 -11.86
        137 -12.24 -32.44
                                5.61 : PRO CG
PRO CB
                                               137 -10.47 -10.47
                              4.13 : PRO O
         137 -11.66 -34.38
PRO C
```

10/32

III 1:10.

```
3.28 : VAL CA 138 -12.31 -12.31
VAL N
         138 -12.58 -34.81
                             1.52 : VAL CG1 138 -13.40 -13.40
                                                                0.11
VAL CB 138 -13.48 -36.17
                                                                0.94
                            2.33 : VAL C
                                            138 -12.06 -12.06
VAL CG2 138 -13.41 -37.40
                                                                1.02
                                            139 -12.78 -12.78
                            0.02 : ASN N
VAL 0
         138 -11.28 -34.37
                            0.07 : ASN CB 139 -14.11 -14.11
                                                                0.03
        139 -12.74 -31.94
ASN CA
                            -0.64 : ASN OD1 139 -16.26 -16.26
                                                               -0.25
        139 -15.11 -32.24
ASN CG
                                            139 -11.75 -11.75
                                                                0.09
ASN ND2 139 -14.75 -32.85
                           -1.75 : ASN C
                                            140 -11.61 -11.61
         139 -11.19 -30.37
                            -0.93 : ASN N
                                                                1.24
ASN O
        140 -10.74 -29.01
                            1.55 : ASN CB
                                           140 -11.22 -11.22
                                                                0.98
ASN CA
                            1.05 : ASN OD1 140 -13.29 -13.29
                                                                2.06
ASN CG
        140 -12.71 -27.61
                             0.00 : ASN C
                                            140 -10.77 -10.77
                                                                3.04
ASN ND2 140 -13.44 -27.87
        140 -11.72 -29.44
                            3.54 : FRO N
                                            141 -9.98 -9.98
                                                                3.90
ASN O
        141 -8.90 -27.39
                                                -9.86 -9.86
                            3.54 : PRO CA
                                           141
                                                                5.32
PRO CD
                                                                4.89
        141 -8.61 -27.99
                            5.78 : PRO CG
                                           141 -8.55 -8.55
PRO CB
                                                                7.49
                            6.27 : PRO 0
                                            141 -10.91 -10.91
        141 -11.01 -28.39
PRO C
                            5.73 : GLN CA 142 -13.34 -13.34
                                                                6.45
        142 -12.13 -27.94
GLN N
                            5.77 : GLN CG 142 -13.23 -13.23
                                                                5.02
       142 -14.15 -26.64
GLN CB
                            5.61 : GLN OE1 142 -14.56 -14.56
                                                                5.48
        142 -13.43 -24.42
GLN CD
GLN NE2 142 -12.42 -23.91
                            6.35 : GLN C
                                            142 -14.21 -14.21
                                                                6.46
                            5.42 : ILE N
                                            143 -14.88 -14.88
                                                                7.56
GLN O
        142 -14.32 -29.46
                            7.60 : ILE CB
                                            143 -15.46 -15.46
                                                                8.92
       143 -15.73 -30.31
ILE CA
                           10.15 : ILE CG1 143 -16.57 -16.57
                                                                9.05
ILE CG2 143 -15.41 -30.26
ILE CD1 143 -16.22 -33.21
                                            143 -17.14 -17.14
                           10.01 : ILE C
                                            144 -18.00 -18.00
                                                                6.68
        143 -17.39 -28.61
                            7.99 : HIS N
ILE O
                            6.45 : HIS CB 144 -19.58 -19.58
                                                                4.99
       144 -19.34 -29.88
HIS CA
                            4.36 : HIS CD2 144 -17.86 -17.86
                                                                3.31
HIS CG
        144 -18.53 -28.73
                            4.68 : HIS CE1 144 -17.01 -17.01
                                                                3.88
HIS ND1 144 -18.00 -27.57
                                            144 -20.32 -20.32
                                                                6.87
                            3.06 : HIS C
HIS NE2 144 -16.95 -28.35
                                            145 -21.40 -21.40
                                                                7.54
        144 -20.12 -32.15
                            6.57 : GLU N
HIS O
                            7.97 : GLU CB
                                           145 -22.62 -22.62
                                                                9.36
       145 -22.39 -31.56
GLU CA
                                            145 -21.37 -21.37
                            9.92 : GLU CD
                                                               11.38
        145 -21.61 -32.31
GLU CG
                           11.80 : GLU OE2 145 -22.34 -22.34
                                                               12.11
GLU OE1 145 -20.21 -32.02
GLU C 145 -23.67 -31.35
                            7.24 : GLU 0
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                            6.57 : PHE CA 146 -25.31 -25.31
        146 -24.10 -32.39
PHE N
                            4.51 : PHE CG 146 -24.19 -24.19
        146 -25.09 -32.99
PHE CB
                            3.63 : PHE CD2 146 -24.76 -24.76
PHE CD1 146 -22.83 -32.34
                            2.77 : PHE CE2 146 -23.96 -23.96
                                                               1.75
PHE CE1 146 -22.04 -31.65
                            1.83 : PHE C
                                           146 -26.38 -26.38
                                                                6.67
PHE CZ 146 -22.61 -30.85
                           6.66 : PHE N
                                                                7.41
                                            147 -27.24 -27.24
PHE O
        146 -26.43 -34.16
                            8.20 : PHE CB 147 -28.77 -28.77
                                                                9.28
       147 -28.25 -32.85
PHE CA
        147 -27.96 -32.05 10.55 : PHE CD1 147 -27.09 -27.09
                                                               10.91
PHE CG
                           11.31 : PHE CE1 147 -26.30 -26.30
                                                               12.03
PHE CD2 147 -28.03 -33.19
                           12.42 : PHE CZ 147 -26.36 -26.36
                                                               12.78
PHE CE2 147 -27.23 -33.35
                                            147 -29.72 -29.72
                                                               6.46
        147 -29.38 -33.14
                            7.26 : PHE O
PHE C
                            7.29 : LEU CA
                                           148 -31.14 -31.14
                                                               6.48
LEU N
        148 -29.97 -34.33
                            6.51 : LEU CG
                                                               5.26
                                           148 -31.58 -31.58
LEU CB
        148 -31.49 -36.11
                            5.53 : LEU CD2 148 -32.29 -32.29
                                                               4.19
LEU CD1 148 -32.43 -38.14
                                            148 -33.33 -33.33
                                                               6.24
                            7.01 : LEU 0
        148 -32.38 -33.95
LEU C
                                                               8.92
                            8.29 : SER CA
                                           149 -33.58 -33.58
        149 -32.37 -33.56
SER N
                                           149 -32.18 -32.18
                                                               10.87
                           10.40 : SER OG
        149 -33.30 -33.21
SER CB
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SER C
        149 -34.53 -31.98
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                                                                8.54
                            8.39 : SER CA
        150 -34.58 -30.69
SER N
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                                                               6.81
                            7.76 : SER OG
        150 -37.05 -30.34
SER CB
                                                               10.59
                                           150 -36.99 -36.99
                           10.00 : SER 0
        150 -36.32 -29.80
SER C
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                                                              12.06
        151 -35.99 -28.67
                           12.85 : THR OG1 151 -33.85 -33.85 12.10
        151 -34.87 -28.95
                                           151 -36.46 -36.46 12.72
THR CG2 151 -34.74 -30.43 13.15 : THR C
THR 0 151 -37.00 -27.46 13.80 : GLU N 152 -36.27 -36.27 12.07 GLU CA 152 -36.43 -24.83 12.73 : GLU CB 152 -37.92 -37.92 13.18
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GLU CG 152 -38.53 -25.06 14.54 : GLU CD 152 -38.34 -38.34 15.68
GLU OE1 152 -38.86 -24.28 16.80 : GLU OE2 152 -37.74 -37.74 15.41
                                           152 -35.53 -35.53 14.96
                           13.88 : GLU 0
        152 -35.43 -24.88
GLU C
                           13.27 : ALA CA 153 -32.93 -32.93 13.81
        153 -34.29 -24.55
ALA N
                                           153 -32.18 -32.18 12.52
                           14.62 : ALA C
       153 -32.52 -25.77
ALA CB
                                           154 -32.53 -32.53 11.68
                           12.22 : GLN N
        153 -31.36 -23.84
ALA O
                                          154 -30.63 -30.63 11.02
                           10.51 : GLN CB
        154 -31.77 -25.92
GLN CA
                                          154 -31.29 -31.29
                                                              10.12
        154 -30.97 -28.24
                           11.41 : GLN CD
GLN CG
                            9.86 : GLN NE2 154 -30.33 -30.33
GLN OE1 154 -32.46 -29.28
                                           154 -31.39 -31.39
                            9.15 : GLN 0
                                                               8.34
        154 -32.29 -26.35
GLN C
                            8.69 : GLN CA
                                                               7.22
                                           155 -33.76 -33.76
        155 -33.50 -26.68
GLN N
                                                               4.93
                                           155 -33.48 -33.48
                            6.45 : GLN CG
        155 -33.41 -25.57
GLN CB
                            4.35 : GIN OE1 155 -35.54 -35.54
                                                               5.03
        155 -34.59 -24.56
GLN CD
                                           155 -33.11 -33.11
GLN NE2 155 -34.53 -24.23
                            3.04 : GLN C
                                           156 -33.85 -33.85
                            6.31 : SER N
        155 -31.92 -28.10
GLN O
                                          156 -34.46 -34.46
                                                               4.97
                           5.33 : SER CB
        156 -33.32 -30.25
SER CA
                                           156 -32.58 -32.58
                                                               4.06
                           4.10 : SER C
        156 -34.05 -32.24
SER OG
                                           157 -31.37 -31.37
                                                               3.75
                            3.24 : TYR N
        156 -33.19 -29.19
SER O
                            2.49 : TYR CB 157 -29.40 -29.40
                                                               2.33
        157 -30.76 -30.07
TYR CA
                            2.37 : TYR CD1 157 -28.82 -28.82
                                                               3.49
        157 -29.27 -32.19
TYR CG
                            3.53 : TYR CD2 157 -29.61 -29.61
                                                               1.27
TYR CE1 157 -28.72 -34.17
                                           157 -29.07 -29.07
                                                                2.42
                            1.30 : TYR CZ
TYR CE2 157 -29.51 -34.25
                                           157 -31.63 -31.63
                                                               1.30
                            2.43 : TYR C
TYR OH 157 -29.03 -36.25
                                           158 -32.64 -32.64
                                                               1.42
        157 -31.46 -29.87
                            0.24 : LEU N
TYR O
                                          158 -34.71 -34.71
                                                               0.75
                            0.34 : LEU CB
       158 -33.60 -31.62
LEU CA
                            0.44 : LEU CD1 158 -33.92 -33.92
                                                               -0.79
        158 -34.74 -34.06
LEU CG
                                                              -0.11
                                           158 -34.32 -34.32
LEU CD2 158 -34.18 -34.87
                            1.58 : LEU C
                                           159 -34.53 -34.53
                                                               0.79
        158 -34.67 -30.20
                           -1.28 : GLN N
LEU O
                            0.45 : GLN CB 159 -35.47 -35.47
                                                               1.68
        159 -35.19 -28.14
GLN CA
                            2.55 : GLN CD 159 -36.61 -36.61
                                                               3.91
        159 -36.42 -28.08
GLN CG
                            4.93 : GLN NE2 159 -37.44 -37.44
                                                               3.94
GLN OE1 159 -36.07 -27.90
                                           159 -35.04 -35.04 -0.99
                           -0.51 : GLN 0
        159 -34.41 -27.27
GLN C
                                           160 -32.50 -32.50
                                                              -1.76
        160 -33.14 -27.46
                           -0.84 : GLU CA
GLU N
                                           160 -30.73 -30.73
        160 -31.04 -26.48
                           -1.45 : GLU CG
GLU CB
                            0.25 : GLU OE1 160 -32.00 -32.00
        160 -31.52 -24.58
GLU CD
                                                              -3.23
                                           160 -32.67 -32.67
GLU OE2 160 -31.65 -23.66
                           -0.59 : GLU C
                                           161 -33.23 -33.23
                                                              -3.47
                           -4.15 : PHE N
        160 -32.28 -26.13
CLU O
                           -4.81 : PHE CB 161 -33.79 -33.79 -4.78
        161 -33.52 -28.52
PHE CA
                                                               -3.56
                           -4.67 : PHE CD1 161 -32.25 -32.25
        161 -32.49 -30.74
PHE CG
                           -5.67 : PHE CE1 161 -31.05 -31.05
                                                               -3.45
PHE CD2 161 -31.58 -30.60
                           -5.56 : PHE CZ 161 -30.14 -30.14
                                                               -4.45
PHE CE2 161 -30.39 -31.25
                                           161 -35.53 -35.53
                                                               -4.50
                           -5.30 : PHE 0
        161 -34.73 -27.77
PHE C
                           -6.60 : SER CA 162 -35.97 -35.97
                                                              -7.03
        162 -34.89 -27.59
SER N
                                           162 -35.27 -35.27
                                                              -9.16
                           -8.44 : SER OG
        162 -35.61 -26.30
SER CB
                                           162 -37.35 -37.35
                           -6.94 : SER 0
        162 -37.31 -27.46
SER C
                                           163 -39.72 -39.72 -6.99
                           -7.21 : LYS CA
        163 -38.45 -26.84
LYS N
                                           163 -41.94 -41.94 -6.24
        163 -40.84 -26.56
                           -7.22 : LYS CG
LYS CB
                                           163 -43.78 -43.78 -8.06
                           -6.74 : LYS CE
        163 -43.08 -25.68
LYS CD
                                           163 -39.90 -39.90 -7.95
                           -8.04 : LYS C
        163 -44.10 -27.66
LYS NZ
                                           164 -39.73 -39.73 -9.25
        163 -40.17 -29.76
                           -7.52 : HIS N
LYS O
        164 -39.92 -29.49 -10.23 : HIS CB 164 -39.64 -39.64 -11.68
HIS CA
        164 -39.24 -30.07 -12.73 : HIS CD2 164 -39.59 -39.59 -14.10
HIS CG
HIS ND1 164 -38.45 -31.19 -12.61 : HIS CE1 164 -38.32 -38.32 -13.78
                                           164 -38.99 -38.99 -9.92
HIS NE2 164 -39.01 -31.07 -14.68 : HIS C
                          -10.14 : ILE N 165 -37.72 -37.72 -9.55
-9.33 : ILE CB 165 -35.45 -35.45 -9.14
        164 -39.39 -31.79 -10.14 : ILE N
HIS O
        165 -36.87 -31.57
ILE CA
ILE CG2 165 -34.53 -31.98 -8.41 : ILE CG1 165 -35.02 -35.02 -10.55
ILE CD1 165 -33.58 -30.40 -10.81 : ILE C
                                           165 -37.40 -37.40 -8.15
                                           166 -37.98 -37.98 -7.11
ILE 0 165 -37.41 -33.62 -8.28 : LEU N
```

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```
LEU CA 166 -38.48 -32.52 -5.97 : LEU CB 166 -38.75 -38.75 -4.84
 LEU CG 166 -37.87 -31.47 -3.61 : LEU CD1 166 -36.66 -36.66 -3.74
 LEU CD2 166 -37.41 -30.07 -3.44 : LEU C
                                           166 -39.74 -39.74 -6.38
         166 -39.85 -34.47 -6.15 : GLU N
                                           167 -40.65 -40.65 -7.09
 LEU O
 GLU CA 167 -41.88 -33.22 -7.51 : GLU CB 167 -42.78 -42.78 -8.24
                           -7.44 : GLU CD 167 -44.52 -44.52 -8.19
 GLU CG
        167 -43.37 -31.11
 GLU OE1 167 -44.47 -30.18 -9.38 : GLU OE2 167 -45.55 -45.55
 GLU C
         167 -41.59 -34.41
                           -8.44 : GLU O
                                           167 -42.08 -42.08
                                                              -8.22
                           -9.38 : ALA CA 168 -40.46 -40.46 -10.34
 ALA N
         168 -40.67 -34.28
 ALA CB 168 -39.68 -34.79 -11.48 : ALA C
                                           168 -39.72 -39.72
                                                             -9.65
                                           169 -38.77 -38.77
         168 -40.04 -37.62
                           -9.85 : SER N
                                                              -8.78
 ALA O
                           -7.99 : SER CB 169 -37.07 -37.07
                                                              -7.08
        169 -38.10 -37.14
 SER CA
        169 -36.02 -35.94
                           -7.82 : SER C
                                           169 -39.05 -39.05
                                                             -7.11
 SER OG
                           -7.32 : PHE N
                                           170 -39.72 -39.72
                                                             -6.14
 SER O
        169 -39.19 -39.13
                           -5.25 : PHE CB 170 -40.81 -40.81
 PHE CA
        170 -40.60 -38.05
                                                             -3.95
                           -3.13 : PHE CD1 170 -38.85 -38.85 -2.68
 PHE CG 170 -39.54 -37.04
 PHE CD2 170 -39.05 -35.79 -2.91 : PHE CE1 170 -37.67 -37.67 -2.01
 PHE CE2 170 -37.86 -35.62 -2.24 : PHE CZ 170 -37.17 -37.17
                                                             -1.80
                                           170 -42.70 -42.70
         170 -41.93 -38.40 -5.87 : PHE 0
                                                             -5.20
 PHE C
         171 -42.20 -37.98 -7.15 : ASN CA 171 -43.44 -43.44
                                                             -7.90
 ASN N
ASN CB 171 -43.57 -39.73 -8.24 : ASN CG 171 -44.74 -44.74
                                                             -9.18
                           -9.87 : ASN ND2 171 -45.21 -45.21
                                                             -9.32
ASN OD1 171 -45.26 -39.16
        171 -44.62 -37.83
172 -44.83 -36.55
                                           171 -45.26 -45.26 -6.40
                           -7.04 : ASN 0
ASN C
                           -6.83 : SER CA 172 -45.90 -45.90 -5.98
SER N
                           -4.50 : SER OG 172 -45.71 -45.71 -3.99
        172 -45.57 -36.23
SER CB
        172 -46.11 -34.56 -6.24 : SER O
SER C
                                           172 -45.29 -45.29 -6.91
        173 -47.28 -34.04 -5.85 : LYS CA 173 -47.49 -47.49 -6.01
LYS N
LYS CB 173 -48.99 -32.46 -6.05 : LYS CG 173 -49.45 -49.45 -7.51
        173 -48.84 -31.14 -8.27 : LYS CE 173 -48.12 -48.12 -9.70
LYS CD
LYS NZ 173 -46.79 -32.04 -9.69 : LYS C
                                           173 -46.74 -46.74
        173 -46.52 -32.54 -3.83 : PHE N
                                           174 -46.22 -46.22
                                                             -5.17
LYS O
                           -4.25 : PHE CB 174 -44.62 -44.62 -4.82
PHE CA 174 -45.24 -30.19
                           -3.79 : PHE CD1 174 -42.48 -42.48 -3.41
PHE CG
        174 -43.66 -28.22
                           -3.08 : PHE CE1 174 -41.73 -41.73 -21.34
PHE CD2 174 -44.03 -27.09
PHE CE2 174 -43.29 -26.63 -2.02 : PHE CZ 174 -42.14 -42.14 -1.65
                                           174 -45.15 -45.15 -1.85
        174 -45.80 -29.98 -2.84 : PHE O
PHE C
        175 -46.96 -29.41 -2.74 : GLU CA 175 -47.58 -47.58 -1.48
GLU N
GLU CB 175 -48.89 -28.45 -1.62 : GLU CG 175 -50.07 -50.07 -2.47
GLU CD 175 -49.50 -29.57 -3.75 : GLU OEL 175 -49.33 -49.33 -3.67
GLU 0E2 175 -49.07 -28.86 -4.71 : GLU C
                                          175 -47.78 -47.78 -0.88
                           0.34 : GLU N
                                           176 -47.91 -47.91 -1.48
        175 -47.70 -30.65
GLU 0
       176 -47.95 -33.04 -0.68 : GLU CB 176 -48.39 -48.39 -1.56
GLU CA
GLU CG 176 -48.15 -35.69 -1.26 : GLU CD 176 -48.70 -48.70 GLU OE1 176 -49.05 -35.53 1.02 : GLU OE2 176 -48.73 -48.73
                                                             0.07
                                                              0.14
                                          176 -46.47 -46.47
                          -0.05 : GLU 0
                                                              1.19
GLU C
        176 -46.56 -33.27
                          -0.86 : ILE CA 177 -44.04 -44.04 -0.46
        177 -45.47 -33.25
ILE N
                          -1.60 : ILE CG2 177 -41.64 -41.64 -1.10
        177 -43.04 -33.02
ILE CB
                          -2.52 : ILE CD1 177 -42.17 -42.17 -3.84
ILE CG1 177 -42.95 -34.20
        177 -43.76 -32.42 0.67 : ILE 0
                                          177 -43.05 -43.05
ILE C
        1.71
ASN N
                           1.15 : ASN CG 178 -43.69 -43.69
                                                             1.96
ASN CB 178 -44.32 -28.95
                           1.36 : ASN ND2 178 -43.77 -43.77
                                                              3.30
ASN OD1 178 -43.06 -26.95
                           3.07 : ASN 0
                                          178 -44.02 -44.02
                                                              4.14
        178 -44.63 -30.59
ASN C
                           3.05 : ARG CA 179 -46.74 -46.74
        179 -45.93 -30.90
                                                              4.23
ARG N
                                          179 -49.14 -49.14
                           3.86 : ARG CG
       179 -48.20 -31.51
ARG CB
                           4.05 : ARG NE 179 -50.02 -50.02
                                                              3.53
ARG CD 179 -50.28 -32.84
                           4.35 : ARG NH1 179 -49.70 -49.70
                                                              3.82
ARG CZ 179 -49.94 -35.31
ARG NH2 179 -50.05 -35.12 5.70 : ARG C 179 -46.15 -46.15
ARG O 179 -45.87 -32.43 6.01 : VAL N 180 -45.89 -45.89
                                                            4.82
                                                            4.03
```

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```
VAL CA 180 -45.38 -34.66 4.73 : VAL CB 180 -45.76 -45.76
                                                                                                                                                  3.89
 VAL CG1 180 -45.60 -35.78 2.39 : VAL CG2 180 -44.82 -44.82
                                                                                                                                                  4.29
                                                               5.13 : VAL O 180 -43.55 -43.55
4.36 : LEU CA 181 -41.53 -41.53
3.34 : LEU CG 181 -39.78 -39.78
                                                                                                                                                 6.21
 VAL C
                   180 -43.89 -34.57
                   181 -42.99 -33.92
 LEU N
LEU CB 181 -40.79 -33.84
                                                                 3.52 : LEU CD2 181 -39.50 -39.50
 LEU CD1 181 -40.23 -36.27
                                                                 5.36 : LEU 0 181 -40.01 -40.01
                   181 -40.99 -32.51
 LEU C
                                                                 5.15 : PHE CA 182 -40.95 -40.95
                   182 -41.55 -31.34
 PHE N
                                                                4.46 : PHE CG 182 -39.44 -39.44
 PHE CB 182 -40.31 -29.33
                                                                 3.94 : PHE CD2 182 -39.73 -39.73
                                                                                                                                                 2.15
PHE CD1 182 -38.40 -30.89
                                                                 3.04 : PHE CE2 182 -38.98 -38.98
PHE CE1 182 -37.66 -31.60
                                                                1.70 : PHE C 182 -41.98 -41.98
                                                                                                                                                  6.23
 PHE CZ 182 -37.95 -31.53
                                                                                                                                                  6.58
                                                                 6.39 : GLU N
                                                                                                   183 -43.21 -43.21
                   182 -41.68 -27.96
 PHE O
                                                                7.08 : GLU CB 183 -45.55 -45.55
7.04 : GLU CD 183 -48.14 -48.14
                                                                                                                                              7.01
 GLU CA 183 -44.16 -28.56
                                                                                                                                              7.08
 GLU CG 183 -46.88 -28.39
                                                                 7.91 : GLU OE2 183 -49.13 -49.13 6.28
 GLU OE1 183 -48.11 -30.36
                                                                                                    183 -43.31 -43.31
                   183 -43.73 -28.16
                                                                 8.52 : GLU 0
 GLU C
                                                                8.57 : GLU CA 184 -43.26 -43.26
                                                                                                                                               9.65
                   184 -43.76 -26.81
 GLU N
                                                                9.22 : GLU CG 184 -42.95 -42.95 10.10
GLU CD 184 -44.00 -22.66 11.05 : GLU OE1 184 -44.07 -44.07 11.05 GLU OE2 184 -44.76 -23.39 11.77 : GLU C 184 -43.79 -43.79 11.02 GLU O 184 -42.96 -26.41 11.92 : GLU N 185 -45.08 -45.08 11.30 GLU CA 185 -45.43 -26.70 12.65 : GLU CB 185 -46.90 -46.90 13.08 GLU CG 185 -46.99 -26.66 14.64 : GLU CD 185 -45.94 -45.94 15.47
 GLU CB 184 -43.51 -24.46
 GLU OE1 185 -44.76 -26.28 15.58 : GLU OE2 185 -46.35 -46.35 16.00
                  185 -44.76 -26.28 15.58 : GLU OEZ 185 -46.35 -46.35 16.00
185 -45.25 -28.21 12.60 : GLU O 185 -45.30 -45.30 11.50
186 -45.01 -28.94 13.67 : GLY CA 186 -44.73 -44.73 13.46
186 -43.27 -30.58 13.06 : GLY O 186 -42.78 -42.78 13.16
187 -42.57 -29.50 12.62 : GLN CA 187 -41.12 -41.12 12.52
187 -40.50 -28.24 12.16 : GLN CG 187 -40.31 -40.31 10.69
187 -39.52 -26.85 10.63 : GLN OE1 187 -38.30 -38.30 10.37
187 -40.12 -25.69 10.96 : GLN C 187 -40.64 -40.64 13.93
187 -41.39 -29.59 14.91 : GLN N 188 -39.35 -39.35 14.08
 GLU C
 GLY N
 GLY C
 GLN N
 GLN CB
 GLN CD
 GLN NE2 187 -40.12 -25.69 10.96 : GLN C
GLN O 187 -41.39 -29.59 14.91 : GLN N 188 -39.35 -39.35 14.08 GLN CA 188 -38.95 -30.45 15.36 : GLN CB 188 -38.47 -38.47 14.97 GLN CG 188 -37.95 -32.96 15.92 : GLN CD 188 -38.88 -38.88 17.09 GLN OE1 188 -39.62 -34.07 17.25 : GLN NE2 188 -38.86 -38.86 18.00 GLN C 188 -37.99 -29.54 16.09 : GLN O 188 -37.27 -37.27 16.85 GLU N 189 -37.78 -28.23 16.04 : GLU CA 189 -36.82 -36.82 16.92 GLU CB 189 -37.18 -27.67 18.44 : GLU CG 189 -38.04 -38.04 18.86 GLU CD 189 -38.38 -26.37 20.37 : GLU OE1 189 -39.57 -39.57 20.73 GLU OE2 189 -37.47 -25.97 21.18 : GLU C 189 -35.32 -35.32 16.84 GLU O 189 -34.54 -27.00 17.38 : GLU C 189 -35.32 -35.32 16.84 GLU O 189 -33.31 -28.93 16.30 : GLY C 190 -32.80 -32.80 16.19 GLY O 190 -33.56 -31.26 16.36 : VAL N 191 -31.52 -31.52 15.94 VAL CA 191 -30.23 -30.73 13.55 : VAL CG2 191 -28.70 -28.70 15.34 VAL C 191 -30.61 -32.61 16.79 : VAL O 191 -30.10 -30.10 16.51
 VAL C 191 -30.61 -32.61 16.79 : VAL 0 191 -30.10 -30.10 16.51

ILE N 192 -30.73 -32.32 18.08 : ILE CA 192 -30.34 -30.34 19.14

ILE CB 192 -29.21 -32.72 20.03 : ILE CG2 192 -29.09 -29.09 21.14

ILE CG1 192 -27.85 -32.61 19.35 : ILE CD1 192 -26.85 -26.85 20.05
ILE CG1 192 -27.85 -32.61 19.35 : ILE CD1 192 -26.85 -26.85 20.05

ILE C 192 -31.65 -33.12 19.86 : ILE O 192 -31.93 -31.93 20.50

VAL N 193 -32.49 -34.08 19.52 : VAL CA 193 -33.88 -33.88 19.95

VAL CB 193 -34.67 -34.82 18.79 : VAL CG1 193 -35.79 -35.79 19.25

VAL CG2 193 -35.32 -33.72 18.02 : VAL C 193 -33.82 -33.82 21.13

VAL O 193 -33.00 -36.07 21.05 : ASN N 194 -34.61 -34.61 22.19

ASN CA 194 -34.53 -36.17 23.13 : ASN CB 194 -34.64 -34.64 24.57

ASN CG 194 -35.99 -35.21 24.89 : ASN OD1 194 -36.50 -36.50 24.14
 ASN ND2 194 -36.52 -35.72 26.01 : ASN C 194 -35.74 -35.74 22.82
                   194 -36.82 -36.56 22.44 : ILE N 195 -35.47 -35.47 22.91
  ASN O
```

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ILE CA 195 -36.53 -39.25 22.68 : ILE CB 195 -36.12 -36.12 21.69 ILE CG2 195 -36.41 -39.57 20.41 : ILE CG1 195 -34.73 -34.73 21.79
ILE CD1 195 -34.46 -41.71 23.06 : ILE C 195 -36.83 -36.83 24.03
ILE O 195 -36.34 -39.35 25.07 : ASP N 196 -37.63 -37.63 24.03
ASP CA 196 -37.98 -41.53 25.27 : ASP CB 196 -39.52 -39.52 25.40
ASP CG 196 -40.08 -42.81 25.97 : ASP CD1 196 -40.21 -40.21 27.21 196 -37.43 -- 37.43 25.38 ASP OD2 196 -40.21 -43.76 25.15 : ASP C 196 -37.40 -43.83 24.50 : SER N 197 -37.22 -37.22 26.67 ASP 0 197 -36.86 -44.22 27.41 : SER CB 197 -37.51 -37.51 28.78 SER CA 197 -37.60 -42.68 29.18 : SER C 197 -37.28 -37.28 26.73 SER OG 197 -36.40 -46.33 26.38 : GLU N 198 -38.60 -38.60 26.48 SER O GLU CA 198 -39.08 -46.78 25.81 : GLU CB 198 -40.60 -40.60 25.64 GLU CG 198 -41.35 -46.78 27.01 : GLU CD 198 -42.11 -42.11 27.37 GLU OE1 198 -41.91 -44.98 28.52 : GLU OE2 198 -42.90 -42.90 26.48 GLU C 198 -38.45 -47.06 24.42 : GLU O 198 -37.90 -37.90 24.27 GLN N 199 -38.43 -46.12 23.43 : GLN CA 199 -37.81 -37.81 22.13 199 -37.74 -45.11 21.28 : GLN CG 199 -39.11 -39.11 -20.94 GLN CB 199 -39.18 -42.89 20.83 : GLN OE1 199 -38.88 -38.88 21.83 GLN CD GIN NE2 199 -39.59 -42.26 19.71 : GIN C 199 -36.38 -36.38 22.25 199 -36.07 -48.15 21.75 : ILE N 200 -35.52 -35.52 23.06 GLN O ILE CA 200 -34.13 -46.81 23.22 : ILE CB 200 -33.47 -33.47 24.42 ILE CG2 200 -31.99 -46.51 24.49 : ILE CG1 200 -33.68 -33.68 24.33 ILE CD1 200 -33.59 -43.99 25.72 : ILE C 200 -33.96 -33.96 23.44 200 -33.10 -48.96 22.80 : LYS N 201 -34.83 -34.83 24.34 ILE 0 201 -34.70 -50.22 24.82 : LYS CB 201 -35.92 -35.92 25.67 LYS GA 26.34 : LYS CD 201 -36.83 -36.83 27.05 LYS CG 201 -35.62 -52.09 201 -36.35 -53.82 28.11 : LYS NZ 201 -37.41 -37.41 29.00 LYS CE 23.74 : LYS 0 201 -33.53 -33.53 23.78 201 -34.53 -51.28 LYS C 22.78 : GLU CA 202 -35.47 -35.47 21.89 GLU N 202 -35.49 -51.25 21.01 : GLU CG 202 -37.04 -37.04 GLU CB 202 -36.76 -52.38 20.75 : GLU OE1 202 -35.44 -35.44 20.69 202 -36.64 -55.03 GLU CD 202 -34.15 -34.15 21.09 GLU OE2 202 -37.47 -55.63 21.48 : GLU C 203 -33.88 -33.88 20.68 21.13 : LEU N 202 -33.33 -53.26 GLU O 203 -32.64 -50.63 19.98 : LEU CB 203 -32.68 -32.68 19.63 LEU CA 203 -31.99 -48.42 18.48 : LEU CD1 203 -31.37 -31.37 19.00 LEU CG 203 -31.39 -31.39 20.84 LEU CD2 203 -30.92 -49.27 17.86 : LEU C LEU O 20.23 : SER N 204 -31.33 -31.33 22.20 203 -30.42 -51.45 204 -30.09 -30.09 24.36 204 -30.06 -50.93 22.91 : SER CB SER CA 204 -29.61 -29.61 22.83 24.62 : SER C SER OG 204 -30.72 -49.47 22.61 : LYS N 205 -30.67 -30.67 204 -28.43 -52.69 SER O LYS CA · 205 -30.57 -54.59 23.03 : LYS CB 205 -31.98 -31.98 23.07 205 -33.66 -33.66 23.17 LYS CG 205 -32.16 -56.55 23.41 : LYS CD 205 -34.57 -55.86 24.09 : LYS NZ 205 -35.57 -35.57 LYS CE 205 -29.80 -55.13 205 -28.68 -28.68 21.92 21.83 : LYS 0 LYS C 206 -30.44 -54.82 20.69 : HIS CA 206 -29.90 -29.90 HIS N 206 -30.87 -54.72 18.31 : HIS CG 206 -30.37 -30.37 HIS CB HIS CD2 206 -30.02 -56.52 16.69 : HIS ND1 206 -30.07 -30.07 HIS CE1 206 -29.55 -55.30 14.97 : HIS NE2 206 -29.52 -29.52 15.47 206 -27.62 -27.62 18.82 206 -28.46 -54.70 19.19 : HIS O HIS C 207 -26.81 -26.81 19.35 207 -28.16 -53.42 19.47 : ALA CA ALA N 207 -25.76 -25.76 20.12 19.86 : ALA C 207 -26.83 -51.46 ALA CB 208 -26.10 -26.10 19.60 : LYS N ALA O 207 -24.74 -54.22 208 -25.85 -25.85 23.68 LYS CA 208 -25.19 -54.66 22.33 : LYS CB 208 -26.66 -26.66 25.65 24.54 : LYS CD 208 -25.67 -53.54 LYS CG 26.82 : LYS NZ 208 -25.33 -25.33 LYS CE 208 -26.62 -52.92 21.89 : LYS O 208 -23.58 -23.58 22.03 208 -24.74 -56.04 LYS C 209 -25.56 -25.56 20.74 209 -25.75 -56.67 21.30 : SER CA SER N 209 -26.86 -58.46 20.24 : SER OG 209 -27.49 -27.49 21.51 SER CB 209 -23.57 -23.57 19.72 209 -24.55 -57.92 19.65 : SER O SER C

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SER N
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   SER CB
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   SER C
            210 -22.69 -56.40 17.84 : SER O
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           211 -22.43 -55.62 18.90 : SER CA 211 -21.06 -21.06 19.26
211 -21.18 -53.82 19.82 : SER OG 211 -22.03 -22.03 19.04
   SER N
   SER CB
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   SER C
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   ARG N
            212 -19.64 -55.88
  ARG CB 212 -19.04 -53.08 21.24 : ARG CG 212 -19.04 -19.04 22.40 ARG CB 212 -19.73 -57.98 22.87 : ARG CG 212 -21.16 -21.16 23.41 ARG CD 212 -21.77 -59.17 22.72 : ARG NE 212 -23.25 -23.25 22.62 ARG CZ 212 -24.10 -59.38 23.70 : ARG NH1 212 -25.47 -25.47 23.54 ARG NH2 212 -23.53 -59.40 24.98 : ARG C 212 -17.62 -17.62 22.00 ARG OT1 212 -16.65 -56.67 22.70 : ARG OT2 212 -17.56 -17.56 21.00
                 -16.65 -56.67 22.70 : ARG 012 212 -17.56

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-5.39 -52.66 28.00 : ASN ND2 220 -4.60

-2.45 -51.28 26.97 : ASN O 220 -1.34

-2.82 -52.06 24.65 : ASN CA 220 -3.41

-2.92 -51.16 28.19 : THR CA 221 -2.36

-3.37 -50.58 30.35 : THR CG1 221 -4.72
  ASN CB
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                                                                    -4.61 27.75
  ASN OD1 220
                                                                     -4.60 28.56
  ASN C
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                                                                    -1.34 26.60
  ASN N
            220
                                                            -3.41 -3.41 25.99
  THR N
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  THR CB
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-0.90 29.67
  THR CG2 221
                  -3.28 -49.38 31.32 : THR C
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                                                            -0.90
                                                                    -0.28 30.16
2.12 29.77
  THR O
                  -0.28 -51.48 29.55 : ILE N
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                                                      222
                                                            -0.28
  ILE CA
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                   1.02 -49.41 30.76 : ILE CB 222
                                                           2.12
  ILE CG2 222
                   2.01 -47.64 29.26 : ILE CG1 222
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  ILE CD1 222
                   4.70 -48.79 29.65 : ILE C 222
                                                                     0.98 31.85
                                                             0.98
  ILE 0
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                                                                     1.49 33.04
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                   1.38 -47.40
                                 34.00 : GLY C
                                                      223
                                                             1.18
                                                                     1.18 35.40
                   0.89 -49.16
 GLY O
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                                                                     1.23 36.42
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                   1.45 -47.62
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                                                             2.90
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                                                             2.60
                                                                     2.60 38.26
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                                 38.28 : ASN C
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                                                                            38.76
 ASN O
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                 -0.55 -46.64
                                  38.42 : GLU N
                                                      225
                                                             1.00
                                                                     1.00
                                                                            39.97
 GLU CA
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                                 40.98 : GLU CB 225
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                                                                     0.87 42.36
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 GLU CG 225
                                 42.87 : GLU CD 225
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                                                                     3.18 42.26
 GLU OE1 225
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                                 41.13 : GLU OE2 225
                                                             4.11
                                                                    4.11 42.99
 GLU C
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                                  40.63 : GLU O
                                                    225
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                                                                    -1.27 41.14
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 PHE N
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                  0.53 -43.83
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                                                                    0.27 39.57
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 PHE CB
           226
                                  39.60 : PHE CG 226
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                                                                    2.30 40.80
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2.97 42.92
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-0.27 37.26
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                                 42.99 : PHE C
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ASN CG
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ASN ND2 228
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                                 35.44 : ASN C
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ASN O
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                                 31.93 : LEU N
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LEU CA
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                -1.54 -44.92
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                                                           -0.13 -0.13 29.09
LEU CG
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                                 26.65 : LEU C
LEU CD2 229
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                                                     229
                                                                   -2.10 28.78
LEU O
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                                                                   -3.25 28.11
THR CA
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                                 27.31 : THR CB
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THR OG1 230
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THR C
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                                                                  -5.11
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GLU N
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GLU CB
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                -1.12 -46.64
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GLU CD 231
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GLU 0E2 231
              -0.18 -43.40 23.45 : GLU C
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GLU O
         231 -3.09 -48.90 23.28 : ARG N
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ARG CA 232 -4.30 -48.65 20.79 : ARG CB 232 -5.79 -5.79 21.15
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1.16.

-8.00 -8.00 22.47 ARG CG 232 -6.85 -47.96 21.46 : ARG CD 232 22.81 : ARG CZ ARG NE -8.92 -47.23 232 232 -8.52 -8.52 23.58 23.79 : ARG NH2 232 -7.35 ARG NH1 232 -9.35 -45.17 -7.35 24.27 -4.25 -48.12 19.35 : ARG O 232 ARG C 232 -4.69 -4.69 19.19 -3.62 -3.62 17.01 -3.73 -48.78 18.28 : THR CA 233 THR N 233 -2.17 -48.08 16.41 : THR OG1 233 -2.13 -2.13 15.30 THR CB 233 -1.14 -48.51 17.43 : THR C 233 -4.57 -4.57 15.98 . THR CG2 233 -4.88 -49.78 16.03 : ASP N -4.97 -4.97 15.02 THR O 233 234 -6.97 -6.97 -5.81 -48.29 13.94 : ASP CB 234 13.64 ASP CA 234 -7.66 -47.55 12.30 : ASP OD1 234 -8.86 -8.86 12.27 ASP CG 234 -4.84 -7.07 -47.39 11.23 : ASP C 234 -4.84 12.80 **ASP OD2 234** -4.30 -47.12 12.60 : ASN N -4.57 235 -4.57 11.96 ASP 0 234 -3.64 -48.91 10.92 : ASN CB 235 -2.35 -2.35 10.86 ASN CA 235 -1.82 9.62 : ASN OD1 235 -1.82 8.80 -1.49 -49.33 ASN CG 235 -4.43 -4.43 9.66 ASN ND2 235 -0.31 -49.97 9.47 : ASN C 235 -5.24 -5.24 9.39 8.98 : SER N -4.34 -50.11 236 ASN O 235 236 -7.12 -7.12 8.20 -6.03 -48.05 8.17 : SER CB SER CA 236 -8.00 -49.08 9.35 : SER C 236 -6.64 -6.64 8.36 SER OG 236 8.30 : LEU N -5.68 -5.68 8.74 -7.88 -46.40 237 SER O 236 -6.75 10.48 9.29 : LEU CB 237 -6.75 LEU CA 237 -5.86 -44.50 11.40 10.16 : LEU CD1 237 -8.96 -8.96 -8.19 -44.14 LEU CG 237 9.69 : LEU C 237 -4.47 -4.47 9.82 -8.38 -42.70 LEU CD2 237 -3.86 -3.86 10.46 -3.94 -43.17 9.64 : ASN N 238 LEU O 237 10.93 : ASN CB -2.50 -45.17 238 -1.67 -1.67 9.68 ASN CA 238 9.03 9.89 : ASN OD1 238 0.29 -0.31 -44.40 0.29 ASN CG 238 -2.52 -2.52 11.91 11.03 : ASN C 238 0.35 -44.56 **ASN ND2 238** -3.45 -3.45 12.86 -1.76 -43.01 11.87 : VAL N 239 238 ASN O -3.76 -43.13 13.90 : VAL CB 239 -5.19 -5.19 13.68 VAL CA 239 -5.83 -41.98 14.85 : VAL CG2 239 -5.14 -5.14 12.56 **VAL CG1 239** -3.58 -43.91 15.20 : VAL 0 239 -3,80 -3.80 15.23 VAL C 239 -3.19 -43.34 16.32 -3.07 -3.07 17.60 LEU N LEU CA 240 240 -0.83 -0.83 19.08 -1.75 -43.57 18.07 : LEU CG 240 LEU CB 240 0.36 -44.71 18.37 : LEU CD2 240 -0.27 19.91 -0.27 LEU CD1 240 -4.50 18.32 -6.14 20.02 -4.27 -43.54 18.44 : LEU O 240 -4.50 LEU C 240 -6.14 -5.13 -44.19 19.24 : ILE CA 241 ILE N 241 -8.50 20.76 -7.53 -44.12 19.92 : ILE CG2 241 -8.50 ILE CB 241 -9.07 18.39 18.52 : ILE CD1 241 -9.07 -8.03 -44.07 ILE CG1 241 -5.86 22.00 21.41 : ILE O -5.86 241 ILE C 241 -5.61 -43.75 21.96 : SER CA 242 -4.23 -4.23 23.26 -4.84 -42.83 SER N 242 23.24 : SER OG 242 -2.74 -2.74 23.89 -2.89 -42.33 SER CB 242 -2.74 -2.74 23.89 -6.08 -6.08 24.03 -5.95 -5.95 26.62 -7.79 -7.79 27.53 -4.61 -4.61 28.18 -3.88 -3.88 29.62 -1.98 -1.98 30.33 -1.32 -1.32 27.55 -5.32 -5.32 30.80 -5.05 -5.05 33.27 -5.74 -5.74 33.88 -5.18 -42.50 24.33 : SER O 242 SER C 242 -4.98 -42.78 25.60 : SER CA 243 SER N 243 26.47 : SER OG 243 SER CB 243 -6.88 -43.62 27.86 : SER O 243 -5.10 -42.48 SER C 243 -4.89 -41.37 28.56 : ILE CA 244 ILE N 244 -2.91 -40.11 29.23 : ILE CG2 244 244 ILE CB -2.14 -40.57 28.08 : ILE CD1 244 ILE CG1 244 -4.58 -40.84 30.91 : ILE 0 244 244 ILE C -4.45 -41.43 32.09 : GLU CA 245 245 GLU N -5.74 33.88 -6.16 -41.71 33.72 : GLU CG 245 - - 5.74 GLU CB 245 -6.88 34.98 34.13 : GLU OE1 245 -6.88 -6.95 -44.08 245 CLU CD -3.96 34.31 -3.96 33.45 : GLU C 245 GLU 0E2 245 -7.98 -43.78 34.40 : MET N 246 -3.86 -3.86 35.02 245 -3.11 -41.63 CLU 0 35.98 : MET CB -1.90 35.55 246 -1.90 -2.83 -39.38 246 MET CA -0.39 33.59 246 -0.39 -0.94 -38.81 34.55 : MET SD MET CG 246 -3.49 37.20 0.79 -36.91 34.78 : MET C -3.49 246 MET CE 246 -3.19 38.46 -4.41 -38.01 36.96 : GLU N 247 -3.19 246 MET 0 -3.96 -38.40 39.44 : GLU CB 247 -4.65 -4.65 40.32 247 GLU CA -2.68 41.69 247 -4.18 -40.09 41.64 : GLU CD 247 -2.68 GLU CG

面.1:17.

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GLU OE1 247
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GLU C
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GLU N
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GLU CB
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GLU CD
             -3.88 -31.72 44.27 : GLU C
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GLU OE2 248
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GLY CA
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GLY O
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ALA CA
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                           37.89 : ALA 0
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ALA C
                                                  4.54
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LEU N
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LEU CB
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                                                          8.27
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LEU CD1 251
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LEU C
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                                                  4.76
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PHE N
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PHE CB
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PHE CD1 252
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PHE CE1 252
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PHE CZ
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              6.27 -36.50
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        252
PHE O
                           32.78 : VAL CB
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              8.57 -37.94
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VAL CA
                                                         9.42 32.40
                           34.70 : VAL CG2 253
                                                  9.42
              9.21 -39.42
VAL CG1 253
                                                          8.31 30.43
              8.95 -37.45
                                            253
                                                  8.31
                           31.39 : VAL 0
        253
VAL C
                                                               32.26
                           31.20 : PRO CD
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PRO N
        254
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                                                 11.78
                           29.89 : PRO CB
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PRO CA
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                            31.58 : PRO C
                                            254
                                                 10.45
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             11.57 -34.89
PRO CG
                           29.06 : HIS N
                                                  9.80
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                                            255
             11.05 -38.25
PRO O
        254
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                                                                27.08
                                                  8.84
                                                          8.84
                           26.73 : HIS CB
                                            255
        255
HIS CA
                                                  6.45
                                                          6.45
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              7.43 -38.77
                           27.09 : HIS CD2 255
        255
HIS CG
                           28.04 : HIS CE1 255
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                                                                27.74
              6.93 -38.04
HIS ND1 255
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                            26.62 : HIS C
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HIS NE2 255
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                           25.28 : TYR N
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HIS O
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TYR CA
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TYR CG .256
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TYR CE2 256
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                           20.59 : TYR C
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TYR OH 256
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              8.97 -40.27
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TYR O
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TYR CA
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TYR CG
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                            21.60 : TYR CD2 257
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                           23.32 : TYR CZ 257
                                                          3.20 22.93
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TYR CE2 257
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TYR OH 257
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                           17.19 : SER CB
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SER O
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LYS CA
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LYS CG
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LYS CE
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                                                   5.56
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LYS C
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ALA N
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ALA O
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ILE CA
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                                                          2.99
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                           15.25 : ILE CG1 261
              1.32 -33.71
ILE CG2 261
                                                                16.92
                           12.57 : ILE C
                                            261
                                                   1.00
                                                          1.00
              2.54 -34.49
ILE CD1 261
                                                          1.05 18.22
              0.04 -36.72 16.40 : VAL N
                                                   1.05
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ILE O
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1

1.18.

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                                                           0.64 20.39
                                                   0.64
 VAL CA 262
             -0.01 -36.27
                                                   1.28
                                                           1.28
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 VAL CG1 262
              -0.32 -36.96
                            21.50 : VAL CG2 262
                                                  -0.20
                                                          -0.20
                                                                 19.65
                                             262
              -0.80 -35.03
                            19.38 : VAL O
 VAL C
         262
                            19.21 : ILE CA
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                                                  -2.99
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                                                                 19.50
              -2.10 -35,06
 ILE N
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                                                  -5.06
                                                          -5.06
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              -4.14 -33.89
                            18.46 : ILE CG2 263
 ILE CB
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             -3.62 -33.72
                            17.05 : ILE CD1 263
                                                  -4.65
                                                          -4.65
                                                                 15.97
 ILE CG1 263
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                            20.86 : ILE O
                                             263
 ILE C
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                            22.00 : LEU CA
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 LEU N
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              -2.75 -33.85
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                            24.43 : LEU CG
                                                                25.11
 LEU CB
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                                             264
                            26.49 : LEU CD2 264
                                                  -2.30
                                                         -2.30
                                                                25.23
              -1.72 -34.21
 LEU CD1 264
              -4.87 -33.28
                            23.67 : LEU O
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                                                          -4.68
                                                                23.58
LEU C
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                            24.07 : VAL CA
VAL N
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              -6.02 -33.78
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                                                  -7.12
                                                         -7.12
                                                                24.48
                                                                22.79
VAL CB
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                            23.50 : VAL CG1 265
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                            24.23 : VAL C
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                                                         -7.40
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VAL CG2 265
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                                                         -7.52 26.81
                            26.21 : VAL N
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VAL 0
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              -7.44 -34.57
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                                                  -6.89
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                                                                 29.18
              -7.68 -32.81
VAL CA 266
                            28.44 : VAL CG2 266
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VAL CG1 266
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             -9.18 -32.85
                            28.40 : VAL 0
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VAL C
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ASN N
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ASN CB
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ASN OD1 267 -11.63 -35.27
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        267 -11.79 -33.61
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ASN C
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        268 -11.17 -33.91
GLU N
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                            33.67 : GLU CG
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GLU CB
                            36.05 : GLU OE1 268 -10.45 -10.45
                                                                36.58
GLU CD
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                                                                33.68
                            36.22 : GLU C
GLU OE2 268 -11.73 -37.79
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                            33.40 : GLY N
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GLU O
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                                                        -7.95
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GLY CA
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             -8.19 -30.31
                            33.69 : GLU N
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                                                  -6.95
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GLY O
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GLU CA
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GLU CG
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                            37.85 : GLU OE2 270
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                                                        -9.21
                                                                35.97
GLU OE1 270
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             -4.56 -30.12
                            35.05 : GLU 0
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GLU C
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ALA CB
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ALA O
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HIS CA
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HIS CG
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HIS ND1 272
                                                                32.44
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                            34.16
                                    HIS C
                                            272
                                                   1.72
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HIS NE2 272
                                  :
                                                          2.03 31.24
                                                   2.03
              2.20 -30.06
                                            273
HIS O
        272
                            32.76
                                    VAL N
                                                  1.88
                                                          1.88 29.05
              2.79 -29.24
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                                    VAL CB
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VAL CA
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                                    VAL CG2 273
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VAL CG1 273
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VAL C
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GLU N
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GLU CB
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GLU CD
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GLU OE2 274
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GLU 0
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LEU CA
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8.66 25.11
9.70 24.59
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LEU CG
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LEU CD2 275
                           25.43 : VAL N
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LEU 0
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                           24.29 : VAL CB 276
24.44 : VAL CG2 276
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VAL CA
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VAL CG1 276
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VAL C
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                                                        11,22 20.83
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             11.26 -27.16
GLY N
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                                                 13.19
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GLY C
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PRO N
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PRO CA
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                                                                 18.44
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 LYS CA
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               14.66 -19.49 19.77 : LYS CD
  LYS CG
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 LYS CD
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 LYS O
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 GLU OE1 283
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 THR O
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 LEU CD2 285
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 GLU OE1 286
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TYR CD2 287
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GLU N
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12.09 24.50
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GLU CD
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              11.35 -19.69
GLU 0E2 288
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GLU O
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SER CA
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             10.80 -24.25 28.45 : SER C
SER OG
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SER O
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              6.65 -23.72 25.39 : TYR CB 290
TYR CA
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TYR CG
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              7.52 -22.22 21.17 : TYR CD2 290
TYR CE1 290
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TYR CE2 290
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TYR OH
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ARG NE
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ARG C
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 GLU CA
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 GLU CG
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 GLU 0E1 293
               1.24 -23.67
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22/32

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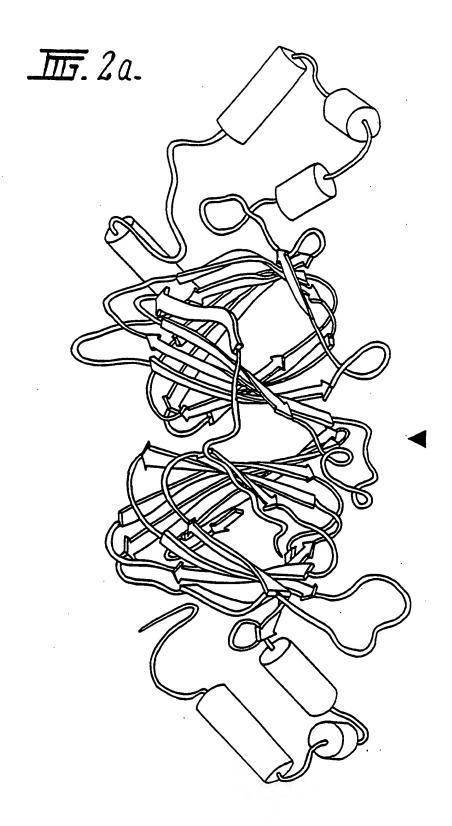
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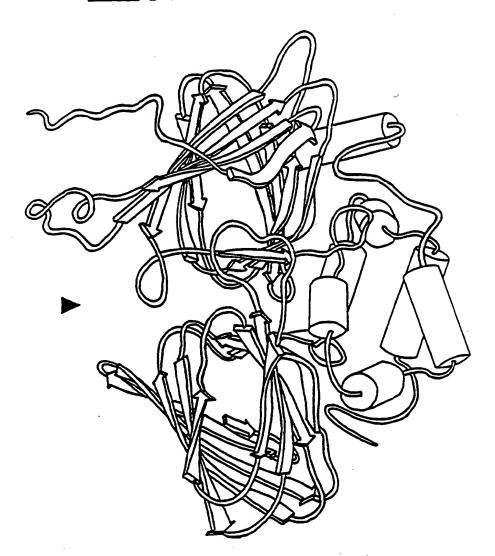
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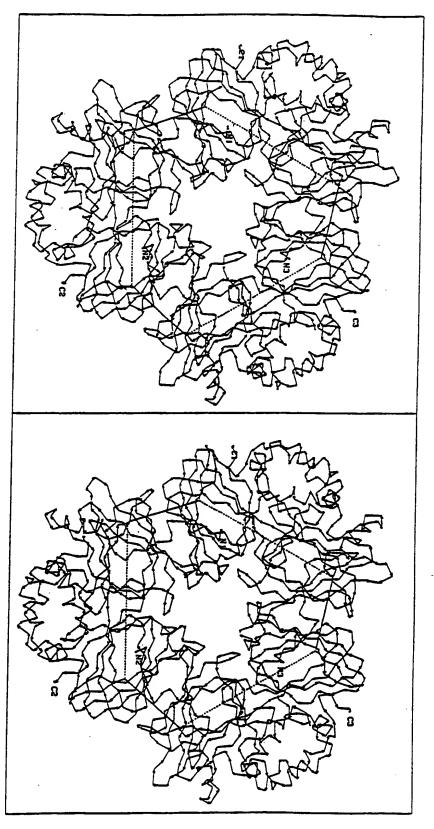
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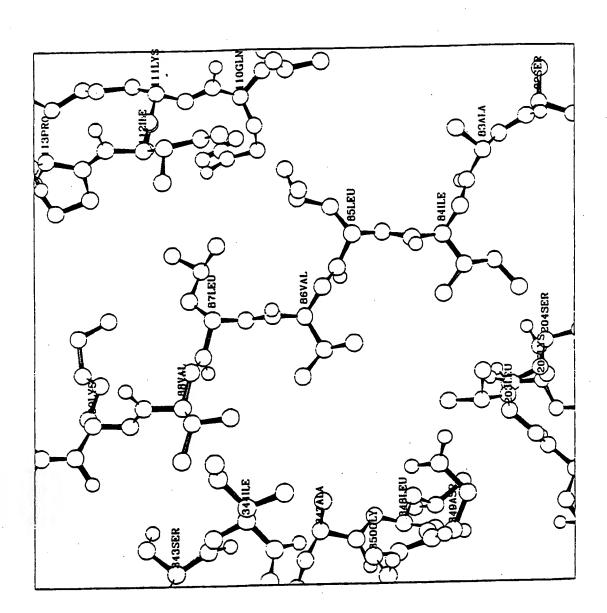


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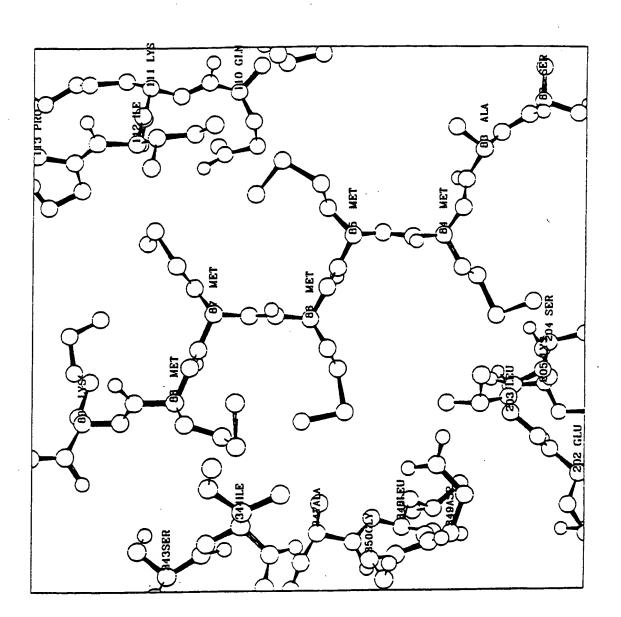


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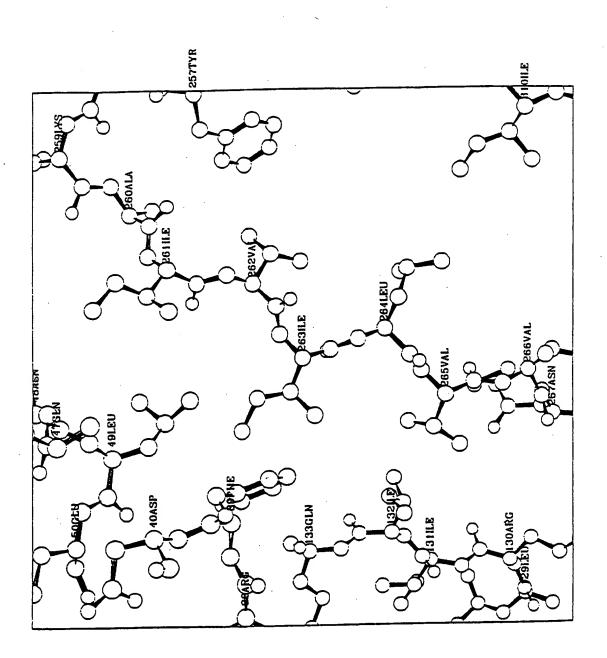


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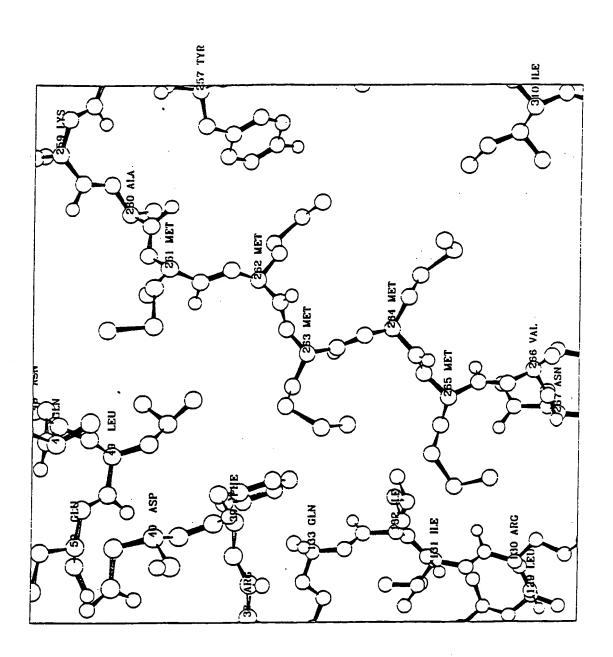


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顶. 5A.



1117. 5B

INTERNATIONAL SEARCH REPORT

International Application No. PCT/AU 90/00430

			1 11 1	
	SSIFICATION OF SUBJECT MATTER (if severat class			
Accordin	g to International Patent Classification (IPC) or to both National Class	sification and IPC	
	5 COTK 13/00, C12N 15/29, A01H 5/00, A01H 5/1	0, 1/00, C12N 1/21 // (C12	N 1/21,C12R 1:01)	
II. FIE	LDS SEARCHED		· 	
		Documentation Searched 7		
Classific	ation System Classificat			
IPC	WPAT, USPM DERWENT DATABASE	KEYWORDS: SEED STORAGE PR	OTEIN	
, , , , , , , , , , , , , , , , , , , 	Documentation Searched other than I to the Extent that such Documents are Incli	linimum Documentation uded in the Fields Searched	18 .	
AU: Cl DATABAS MODIFIC	2N 15/29, CO7K 13/00; CHEMICAL ABSTRACTS KEYW E KEYWORDS AS ABOVE, ADDITIONAL KEYWORDS: MUT CATION	ORDS AS ABOVE AND BIOTECHN EIN, MUTANT, VARIANT, MODI	CLOSY DERWENT FIED,	
III. DOC	LIMENTS CONSIDERED TO BE RELEVANT 9			
Category*	Citation of Document, with indication of the relevant passages	, where appropriate, 12	Relevant to	
P,A	Protein Engineering, volume 3, no. 8, 1990, Shick Kim et al., "Improvement of nutrition properties of soybean glycinin by protein endocument.	al value and functional	(1-13)	
A	Plant Molecular Biology, vol 11, 1988, pp. Hoffman et al., "A modified storage protein processed, and degraded in the seeds of tran whole document.	in is synthesized,		
A	Biochem. Physiol. Pflanzen, 183, 1988 pp. 2 et al., "Construction of storage protein genumber of methionine codons and their use in experiments", whole document.	nes with increased	(1-16)	
* Spe	cial categories of cited documents: 10 "T"	later document published		
"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or "X" after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or "Y"		claimed invention cannot be considered novel or cannot be considered to involve an inventive step		
"O" document referring to an oral disclosure, involve use, exhibition or other means is combi "P" document published prior to the document international filing date but later than a person		involve an inventive steris combined with one or documents, such combinat a person skilled in the	olve an inventive step when the document combined with one or more other such uments, such combination being obvious to erson skilled in the art. ument member of the same patent family	
IV. CER	TIFICATION			
Date of t	he Actual Completion of the	Date of Mailing of th	is International	
	onal Search 7 1991 (03.01.91)	Search Report	1991	
	onal Searching Authority	Signature of Authority	ed Officer	
Australia	n Patent Office	M.E. KEESE	_	

FURTHER	INFORMATION CONTINUED FROM THE SECOND SHEET	101/20 30/004
A	Nature, volume 339, 29 June 1989, pp. 658-659, Dagmar Ringe, "The sheep in wolf's clothing", whole document.	(1-13)
A	Fed. Proc. Fed. Am. Soc. Exptl. Biol; vol 46, 6, p. 2023 C.D. Dickinson et al., "Engineering of soybean seed storage proteins", abstract.	(1-13)
۷. []	OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE 1	

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

- 1.[] Claim numbers ..., because they relate to subject matter not required to be searched by this Authority, namely:
- 2.[] Claim numbers ..., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
- 3.[] Claim numbers ..., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4 (a):

VI. [] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING 2

This International Searching Authority found multiple inventions in this international application as follows:

- [1. [] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
- [] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
- | 3. [] No required additional search fees were timely paid by the applicant. Consequently, this
 international search report is restricted to the invention first mentioned in the claims;
 it is covered by claim numbers:
- 4. [] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

| Remark on Protest

- [] The additional search fees were accompanied by applicant's protest.
 - No protest accompanied the payment of additional search fees.

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